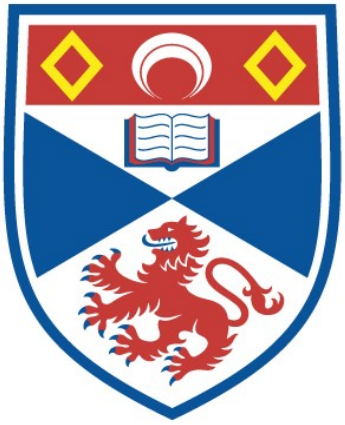
TETRA- AND PENTA-VICINALLY FLUORINATED CYCLOHEXANE RING MOTIFS

Tetiana Bykova

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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Tetiana Bykova

University of
St Andrews

This thesis is submitted in partial fulfilment for the degree of

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Abstract

Organofluorine compounds have had an important influence on the advances in the healthcare and agricultural industries. Selective substitution with fluorine can produce a significant impact on the pharmacokinetic properties of bioactive compounds; generally this is through stereoelectronic effects that the fluorine atom can confer. As such, there is a continuous interest in the development of novel organofluorine compounds and the incorporation of fluorine into bioactive compounds and natural products.

The all-*cis*-1,2,4,5-tetrafluorocyclohexane motifs were the first examples of facially polarised cyclohexane rings which possess a dipolar nature arising from two 1,3-diaxial C-F bonds. The fluorine face, which possesses a negative electrostatic profile, along with the positively polarized methylene hydrogens on the opposite face give a unique facial polarity to this motif.

These highly polarized fluorinated ring systems present as novel building blocks for use in drug development and agricultural programs; hence the aim of this study was the development of functionalised derivatives of these all-*cis* tetrafluoro-cyclohexanes. Transformations of previously reported phenyl all-*cis*-2, 3, 5, 6-tetrafluoro-cyclohexane were explored in a variety of directions and new pathways towards partially fluorinated cyclohexanes were investigated. The range of all-*cis*-tetrafluorocyclohexane motifs produced, with functional groups attached directly to the fluorinated cyclohexane ring, varied from methyl substituted all-*cis*-tetrafluorocyclohexane alcohols, aldehydes, nitriles and amines to all-*cis*-tetrafluorocyclohexane amino acid, pentafluoro carboxylic acid and alcohol derivatives.

These novel derivatives were then used in liquid-phase peptide synthesis, incorporated into peptidomimetic systems through Ugi multi-component reactions and utilised in the formation of *bis*-systems, in order to demonstrate their reactivity and to gain an insight into their possible intramolecular conformational preferences and supramolecular arrangements.

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My entire PhD and the work that has gone into this thesis would be anything but just my own. Firstly, I would like to thank everyone who has been a part of this journey.

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I am very grateful to the past and present members of the DOH group for their invaluable support and contributions to this work. Profound appreciation goes to Dr Nawaf Al-Maharik for guidance in organic chemistry, particularly through the beginning of the project. Dr Philip Lowe for bravely proof reading this Thesis. Maria and Nouchali for productive discussions and keeping me sane writing. Davide, Ricardo, Axel, Hedi, Stephen, Qing, Josh, Fang, Neil, Fatah, Xuan, Cihang for their support and a great time in the lab. Completing this work would have been all the more difficult were it not for the support and friendship provided by the other members of the department including Nastya, Nicolas and all of the Lassio football team. I wish them all best of luck for the future.

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Abbreviations

ATP	adenosine triphosphate
Bn	benzyl
c	concentration
cat.	catalytic
COSY	correlation spectroscopy
CPCM	polarizable continuum model
d	doublet
Da	dalton
DAST	(diethylamino)sulfur trifluoride
DCM	dichloromethane
Deoxofluor®	bis(2-methoxyethyl)aminosulfur trifluoride
DFT	density functional theory
DFMBA	N,N-Diethyl-α,α-difluoro(meta-methylbenzyl)amine
DNA	deoxyribonucleic acid
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DIPEA	N,N-Diisopropylethylamine
dUMP	deoxyuridine monophosphate
dTMP	deoxythymidine monophosphate
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
eq.	equivalents
ES	electrospray
ESI	electrospray ionisation
E1cB	elimination unimolecular conjugate base
E1	unimolecular elimination
E2	bimolecular elimination
FARs	α-fluoroamines
^{18}F-FDG	2-Deoxy-2-^{18}F-fluoro-β-D-glucose
Fluolead™	4-tert-butyl-2,6-dimethylphenylsulfur trifluoride
HFCH	hexafluorocyclohexane
HMBC	heteronuclear multiple bond correlation
HMG-CoA reductase	3-hydroxy-3-methylglutaryl-CoA reductase
HOMO	highest occupied molecular orbita
HOBt	1-Hydroxybenzotriazole
HPLC	high performance liquid chromatography
HSQC	heteronuclear single quantum coherence spectroscopy
IBX	2-iodoxybenzoic acid
IR	infrared
J	coupling constant
K	kilo, 10^3
KF	potassium fluoride
LC-MS	liquid chromatography-mass spectrometry
LDL	low-density lipoprotein
LUMO	lowest unoccupied molecular orbita
L-Selectride	Lithium tri-sec-butylborohydride
m.p.	melting point
m	multiplet

M	molar
M	molecular ion
*m*CPBA	*meta*-chloroperoxybenzoic acid
MS	mass spectrometry
Min	minutes
NAD+	nicotinamide adenine dinucleotide (oxidized form)
NADH	nicotinamide adenine dinucleotide (reduced form)
NADP+	nicotinamide adenine dinucleotide phosphate (ox. form)
NADPH	nicotinamide adenine dinucleotide phosphate (red.form)
NBS	N-bromosuccinimide
NCEs	new chemical entities
NFSI	N-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
PGI_2	prostacyclin
PE	petroleum ether
PET	positron emission tomography
ppm	parts per million
PyFluor	2-pyridinesulfonyl fluoride
Py.HF	Olah's reagent, Pyridine hydrofluoride
PPDA	perfluoropropene–diethylamine
quant.	quantitative
r.t.	room temperature
Rf	retention factor
SSRI	selective serotonin reuptake inhibitor
Selectfluor	S-adenosylhomocysteine S-adenosyl-L-methionine 1 chloromethyl-4-fluoro-1,4- diazoniabicyclo[2.2.2]octane
SAR	structure-activity relationship
TBAF	tetrabutylammonium fluoride
TMAF	tetramethylammonium fluoride
TBDPS	tert-butyldiphenylsilyl
TBDPSCl	tert-butyl diphenylchlorosilane
TBTU	tetramethyluronium tetrafluoroborate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFEDMA	1,1,2,2-tetrafluoroethyl-N, N-dimethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl, para-toluenesulfonyl
TS	thymidylate synthase
TsCl	tosyl chloride, para-toluenesulfonyl chloride
UV	ultraviolet
w/v	weight per volume
δ	chemical shift
4-UCR	Ugi four-component reaction
XtalFluor-E®	diethyl aminodifluorosulfinium tetrafluoroborate
5-FU	5-fluorouracil

Contents

Chapter 1. Introduction.

Organofluorine compounds have been employed successfully across much of the chemical industry but particularly in the fields of pharmaceutical, polymer, agrochemical and materials chemistry.[1,2] Within the pharmaceutical's field the involvement of fluorine has been particularly prominent, as one fifth of all drugs on the market contain at least one fluorine atom.[3,4] The fluorinated polymer TeflonTM is a high profile example of a wide range of organofluorine materials and it is used in many different applications such as in cookware and for wiring in aerospace and computer applications.[3,5–7] The breadth of use for organofluorine compounds extends far beyond that mentioned above and arise because of the unique properties of fluorine.

1.1. The properties of fluorine.

1.1.1. Electronegativity.

Fluorine is the most electronegative element, with assigned electronegativity value of χ=4 by Linus Pauling (Table 1). Pauling described electronegativity as "the power of an atom in a molecule to attract electrons to itself".[8,9]

	H	Si	C	P	N	S	O	Cl	**F**
Electronegativity (χ)	2.1	1.8	2.5	2.1	3.0	2.5	3.5	3.0	**4.0**
Van der Waals radii/A°	1.2	2.1	1.7	1.8	1.55	1.8	1.52	1.74	**1.47**
Bond lengths to Carbon/ A°	1.09	1.85	1.54	1.84	1.47	1.82	1.43	1.77	**1.35**
Bond dissociation energy/kcal mol^{-1}	98.8		83.1		69.7		84.0	78.5	**105.4**

Table 1.1: Electronegativities on the Pauling scale, the van der Waals radii (Bondi)6 and average C–X bond lengths of some common elements.[6,8,9]

Such a high electronegativity is exemplified by the position of fluorine in the Periodic Table, where it has the smallest atomic radius among the Period 2 elements and the second highest nuclear charge (after noble gas neon) with nine protons. Generating F^+, by removing one of the 2p electrons from fluorine ($1s^2$, $2s^2$, $2p^5$) is challenging as these electrons are held very tightly by the nuclear charge with a first ionization energy of 402.15 kcal/mol. In order

to fill the 2p orbital, fluorine will readily accept an electron to balance the nuclear charge, which in turn makes it sterically compressed. As we move down the Periodic Group, the electronegativity of the halogens decreases due to the valence electrons lying in higher shells and further away from the nucleus.

1.1.2. Hydrogen Bonding.

Hydrogen bonding with organic fluorine, where fluorine acts as a hydrogen bond acceptor has been a subject of debates for over 30 years. As this interaction consists of electrostatic forces, deriving from charge transfer between the donor and the acceptor, it follows that due to it's lone pairs being held tightly by the nucleus fluorine is a weak hydrogen bond acceptor and a poor van der Waals participant in organic molecules. The average van der Waals radius between fluorine and hydrogen is 2.5 -2.7 Å, and only on very rare occasions (X-ray data structures) is the CF--HX distance less than 2.3 Å.[10] Due to the weakness of the X–H···F–C hydrogen bonds, it is nessesary to examine these electrostatic interactions with multiple techniques in order to verify a new hydrogen bond interactions.

In some studies it has been shown that hydrogen bonding is observed in aprotic solvents if competing hydrogen bond to solvent is removed. For example in levoglucos (**1.1**), NMR analysis in an aprotic solvent of non-fluorinated 4-deoxy levoglucosan (**1.1**), had a $^{3}J_{H2\text{-}OH}$ of 10.2 Hz (Figure 1.1). [11,12] This corresponds to a torsion angle H-C(2)-O-H of 157° (Figure 1.1). Introduction of a fluorine atom at C-4 (4-deoxy-4-fluorolevoglucosan, 1.2), had a $^{3}J_{H2\text{-}OH}$ value of 11.5 Hz, which corresponds to an increased dihedral angle H-C(2)-O-H (with calculated value of 177.6°), indicating intramolecular hydrogen bonding.[11,12]

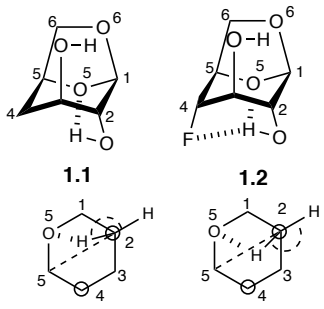


Figure 1.1: 4-Deoxylevoglucosan (1.1) and 4-deoxy-4-fluorolevoglucosan (1.2).

Grimme *et al.* demonstrated in the series of molecules CH_3F---CH_4, CH_3F---C_2H_4 and CH_3F---C_2H_2 the interaction energy increases in going from C(sp3)-H to C(sp2)-H to C(sp)-H, H-bond donors and CH_3F acceptor following an increase in the s-character of the donor C-H bond. This is consistent with electrostatic interactions between the more polarised C-H bond and

fluorine. [13]

In studies descrived by Dalvit and Vulpetti, the correlation between the ^{19}F NMR chemical shifts of fluorine and X-ray analysis of the fluorine–protein interactions has shown that fluorine atoms with increased electron density have better ability to engage in hydrogen bond by being in close proximity to hydrogen bond donors. [14] Dieshielded fluorines on the other hand, were found to orientate towards hydrophobic side chains. In addition to the experimental studies, the computational quantum chemical methods also supported the proposed "rule of shielding".[14]

As in general, there have been enough studies conducted in support of organic fluorine being a hydrogen bond acceptor. However it is important to recognise that due to weak binding energies of X–H···F–C hydrogen bonds, in addition to crystallographic analysis, both computational and spectroscopic experiments are nessesary to analyse the same system in order to show the presence of hydrogen bonding. [14]

1.1.3. The size of fluorine

The size of a fluorine atom lies closest to that of hydrogen for any element that has a monovalent attachment to carbon (Table 1.1). This makes it the best candidate in organic chemistry for the replacement of hydrogen. This is especially useful in drug discovery programs, where pharmacokinetic properties of lead compounds can be modified by such a substitution, while the steric profile of the molecule remains relatively unaffected. While substitution of hydrogen by fluorine offers an electronic torque through a molecule, replacement of electronegative O by F, doesn't induce such a significant change in its electrostatic profile. In the case of C=O for CF_2, a change of hybridisation at carbon is observed and this is a substantial change, which is generally not useful. Swapping C-OH with C-F, means the loss of a hydrogen bond donor. An OH for F replacement can clearly alter the intermolecular hydrogen bonding between a drug candidate and the active site of the target protein. As such, this can offer a useful tool in studying the effect of the polarity of the C-OH on a system in comparison to the hydrogen bonding interactions, as C-F retains the polarity, has no H-bond donor ability and in only a weak hydrogen bond acceptor.[1,15]

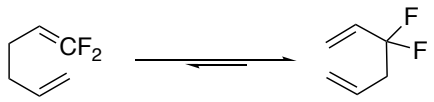
1.2. C-F bond.

The C-F bond is highly polarised with most of the electron density focused on fluorine. Due to its high electronegativity, there is a strong electrostatic attraction between the carbon δ^+ and fluorine δ^- atoms in the covalent C-F bond.[16] The bond has more ionic character than a

classic covalent bond and this makes the bond the strongest in organic chemistry.[17] The polarity of this bond gives rise to a strong dipole moment, which consequently can interact with other dipoles associated with functional groups in the same molecule, to adopt the most energetically favorable conformation of the molecule.

A study by Wiberg and Rablen has shown how increasing the number of fluorine atoms for hydrogen on a carbon atom, going from fluoromethane to tetrafluoromethane, sequentially shortens the C-F bond length.[18] From CH_3F to CF_4, the negative charge is consistent on the additional fluorine atoms, while there is a progressive increase in the positive charge on the carbon atom, which leads to the observed bond shortening and associated geometrical changes.[1,18]

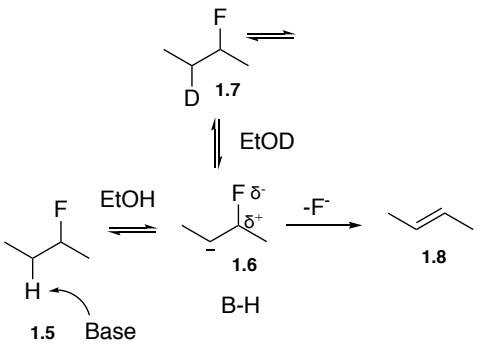
Another observation is a clear preference for fluorine to bond to sp^3 rather than to sp^2 hybridised carbon atoms. Dolbier *et al.* demonstrated that 3,3-difluoro- 1,5-hexadiene (**1.4**) is preferred to 1,1-difluoro-1,5-hexadiene (**1.3**), during the Cope rearrangement (Scheme 1.1).[19] This can be explained by the electronegativities of the carbon atoms, where the sp^3 carbon is less electronegative then sp^2 carbon and thus a stronger bond is formed to the sp^3 carbon as the fluorine can withdraw more electron density .



1.3 **1.4**

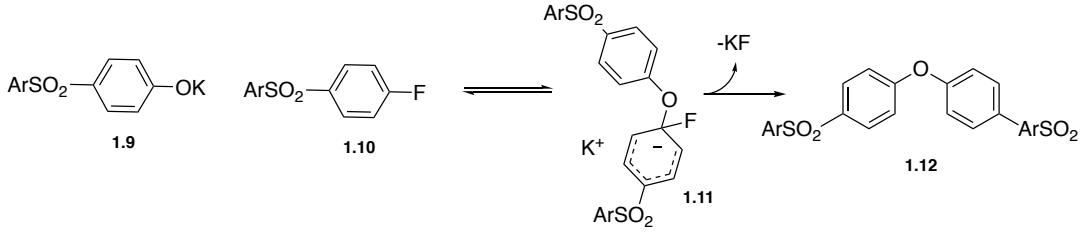
Scheme 1.1: Cope rearrangement of 1,1-difluoro-1,5-hexadiene (1.1) to form 3,3-difluoro- 1,5-hexadiene (1.2).[19]

Fluorine tends to undergo E1cB rather then E2 elimination reactions. A study on such a reaction is shown in Scheme 1.2, whereby deprotonation of the β- hydrogen in 2-fluorobutane **1.5**, leads to the intermediate anion **1.6**, which is stabilised by the electronegativity of the fluorine and can undergo reversible deprotonation.[1,15] This propensity to elimination is often a problem during the synthesis of C-F containing molecules.



Scheme 1.2: E1cB type elimination reaction of in 2-fluorobutane (1.5) to form but-2-ene (1.8). [1]

One of the most common examples of C-F bond cleavage is found during nucleophilic aromatic substitution reactions, again proceeding via a two-step process. For example in the ether synthesis shown in Scheme 1.3, the aromatic ring is attacked by a nucleophile generating a stabilised meisenheimer intermediate (**1.11**) and then subsequent elimination of the fluoride ion.[20]



Scheme 1.3: C-F bond cleavage in nucleophilic aromatic substitution reaction. [20]

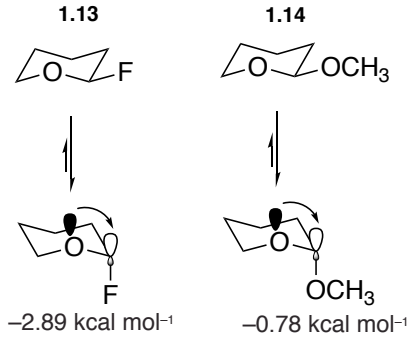
1.3. Stereoelectronic effects of C-F bond.

1.3.1. Hyperconjugation and the 'gauche' effect.

When the C-F bond is selectively introduced into organic molecules, it can induce a significant impact on the molecular conformation through hyperconjugation, dipole - dipole and dipole - electrostatic interactions.

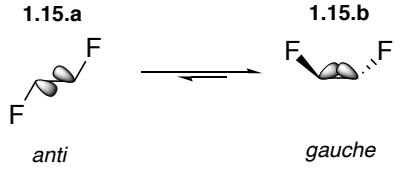
The highly polar nature of the C-F bond lowers the energy of the antibonding orbital ($\sigma^*_{C\text{-}F}$), which is located 180° to the $\sigma_{C\text{-}F}$. The low-lying $\sigma^*_{C\text{-}F}$ can therefore act as a good electron acceptor and can accommodate electron density in the form of lone pairs, electron rich π-bonds or covalent bonds such as C-H. A study on anomeric effects has been demonstrated by Pinto *et al*, revealing that the $\sigma^*_{C\text{-}F}$ of 2-fluorooxacyclohexane (**1.13**, see Scheme 1.3) behaves in a similar manner to the $\sigma^*_{C\text{-}O}$ in 2-methoxyoxacyclohexane (**1.14**). .[21] Density

functional theory (DFT) molecular orbital calculations of these molecules revealed a C-F/O bond elongation and O-C bond shortening in going from the equatorial to the axial conformation. Along with bond length, the stabilization energy ΔE is favoured by –2.89 for kcal mol^{-1} for **1.13** and -0.78 kcal mol^{-1} for **1.14**, which clearly shows that there is an axial preference in both cases. This can be rationalised by hyperconjugative donation of lone pair on oxygen into the LUMO $\sigma^*_{C\text{-}O\ or}\ \sigma^*_{C\text{-}F}$ as shown on Scheme 1.4.



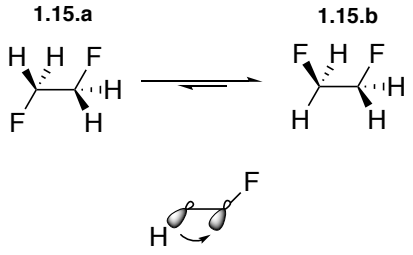
Scheme 1.4: Conformational preferences and anomeric effects of 2-fluorooxacyclohexane (1.13) and 2-methoxyoxacyclohexane (1.14). [21]

Wolfe *et al.* highlighted the *gauche* preference of 1,2-difluoroethane.[22] Durig *et al.* has supported this observation, showing spectroscopically (for IR/Raman), that the *gauche* rotamer dominates over the *anti* by 2.4-3.4 kJ/mol (**1.15.b**, see Scheme 1.5).[22–25] There are several hypothesis that have been accounted for this observation. Initially Wiberg discussed a 'bend bond model', where the preference for the *gauche* rotamer arises from destabilsation of the *anti*-rotomer (**1.15.a**). This explanation lies in the polarisability of the C–F bond, where the degree of bond bending is proportional to the electronegativity of the substituent. The electron rich C–C bond orbitals are directed towards the fluorine atom. In the case of the *gauche*-rotamer, bond bending would occur in the same direction, while in the *anti*-rotamer, bonds are being bent in opposite directions leading to lower orbital overlap.[26]



Scheme 1.5: Bond bending theory of preferred gauche conformation. [22–25]

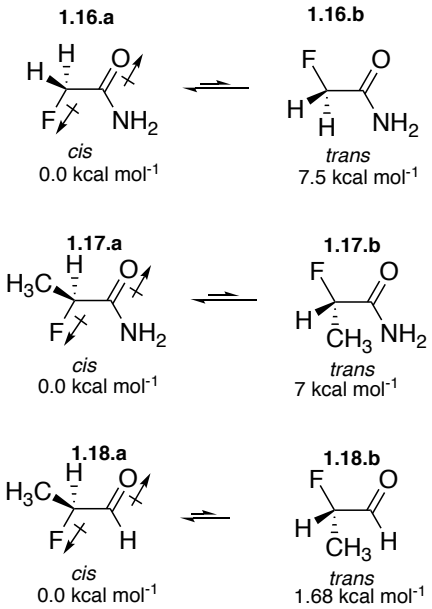
An alternative and more enduring explanation is hyperconjugation.[27] This is explained in terms of HOMO-LUMO interactions, whereby in the *gauche* conformation, the σ* antibonding orbital of C-F receives electron density (hyperconjugation) from σ C-H bond, which lies antiperiplanar to the vicinal C-F bond (Scheme 1.6). [28]



Scheme 1.6: Hyperconjugation of 1,2-difluoroethane. [28]

1.3.2. Dipole-Dipole interactions.

The relatively large dipole moment (μ) of the C-F bond arises from the electronegativity of fluorine and the consequent ionic character of the bond. This can induce a significant influence on molecular conformation as well as intermolecular interactions in protein/enzyme binding interactions.[29,28]



Scheme 1.7: α-fluorocarbonyl derivatives with diapole moments and calculated energy differences between *cis* and *trans* conformations. [30]

In the case of fluoroacetamide (**1.16** and **1.17**), the C-F bond prefers to lie *trans* and antiparallel to the carbonyl and on the same plane to the N-H bond of the amide. The energy difference between *cis* and *trans* conformations is ≈7.5 kcal mol^{-1} (Scheme 1.7).[30] Due to opposed C-F and C=O bond dipoles, the dipole moment is also lower for the *trans* conformer, which has a dipole moment of 2.1 D in comparison to *cis* conformer, which dipole moment is 4.8 D. There is also an electrostatic interaction between F and HN, reinforcing the dipole-dipole interaction from the opposing carbonyl and C–F bonds (Scheme 1.7). The preference for the *trans* conformation decreases with decreasing dipole of the carbonyl. This is consistent with α-fluoroaldehydes such as **1.18**, which have the lowest preference.[30]

Crystallographic analysis conducted by Diederich *et al.*, explored the binding of fluorinated ligands to enzymes such as thrombin.[29,31] The X-ray study of several thousand structures revealed intermolecular C–F···C(O)N contacts, where the fluorine was statistically found to approach along a pseudotrigonal axis to the amide carbonyl. This can be rationalised in terms of advantageous interactions between the C–F and the carbonyl dipoles of the peptide backbone (Figure 1.2).[31] In drug development programs, this effect may offer a small advantage in binding energies to the target protein.

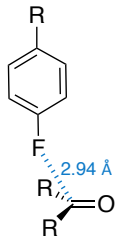
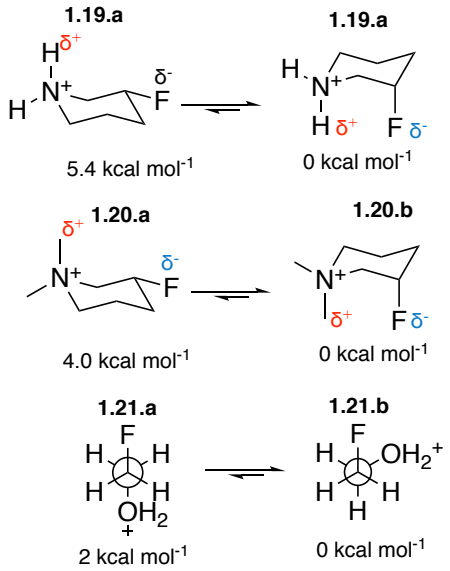


Figure 1.2: Typical orientation of C-F bond to the amides of the protein.[31]

1.3.3. Charge-Dipole interactions.

Charge-dipole interactions are one of the most energetically significant interactions that occur between a C-F bond and adjacent groups, when a group has a formal charge. Snyder *et al.* highlighted 3-fluoropiperidine (**1.19**, Scheme 1.8) and N-methyl-3-fluoropiperidinium salts (**1.20**) in this context. [32] There is a significant preference for fluorine to lie in the axial, rather than equatorial position (Scheme 1.8). Theory studies estimate that the preference for an axial fluorine is 5.4 kcal mol^{-1} in **1.19** and 4 kcal mol^{-1} in **1.20**. This was consistent with NMR and X-ray analysis.[32]



Scheme 1.8: Conformational preferences of: 3-Fluoropiperidine (1.19); N-Methyl-3-fluoropiperidinium Salts (1.20); 2-fluoroethanol (1.21). [32, 33]

For protonated 2-fluoroethanol (**1.21,** Scheme 1.8), where the oxygen has a formal positive charge, it was also demonstrated that the preferred conformation, positions fluorine close to the positively charged oxygen, with a preference of 2.0 kcal mol^{-1}. This indicates significant electrostatic charge-dipole interactions (Scheme 1.8).[33]

1.3.4. 1,3- Dipolar repulsions.

Another conformational effect of more highly fluorinated compounds is observed as a result of dipolar repulsion between C-F bonds. This is clearly seen in the work conducted by Sun *et al.* investigating the conformational properties of 1,3-difluoropropane.[34] A*b initio* calculations of **1.22**, indicate that the order of conformational energies was established by both *gauche* effect attraction and dipolar repulsion effects. As illustrated in Figure 1.3, the stabilization increases as we go from **1.22.a** to **c**, where the pattern follows the δ C-H to δ* C-F hyperconjugation *gauche* effect, the most favorable being **1.22.a**. This conformation has two δ C-H to δ* C-F interactions, followed by **b** and **c**, with one and none. However, **1.22.d** which, also with two δ C-H to δ* C-F interactions, possesses the highest energy conformation of 3.3 kcal mol^{-1}. This can be explained by dipolar repulsion between the C-F bonds, which dominates the hyperconjugation interactions.

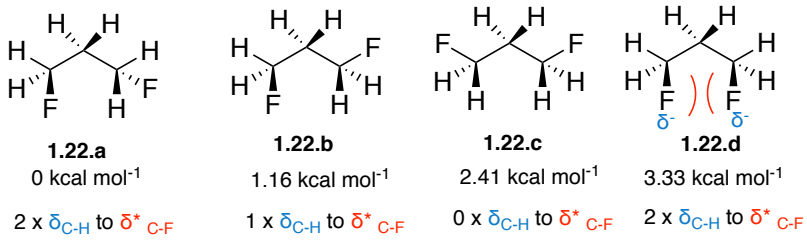


Figure 1.3: Stabilisation energy profile of 1,3-difluoropropane (1.22).[34]

The concept of dipolar repulsion overriding hyperconjugative interactions has been explored by the St Andrews group. This work revealed that linear chains of stereoisomers with fluorines positioned *all-syn*-to each other, such as hexafluoro stereoisomer **1.23** (see Figure 1.4), adopt a helical arrangement.[1,35] The preference for helical over *anti*-zigzag, which was observed for the hexafluoro stereoisomer **1.24**, indicates that in **1.23** both 1,2-*gauche* effects and 1,3-dipolar repulsions play an important role in the molecular conformation.[35] In this instance C-F bonds positioned 1, 2 to each other are aligned *gauche*, while no 1, 3 C-F bond alignments occurs.[17] This indicates that C-F dipoles can interact sufficiently strongly to dictate conformation.

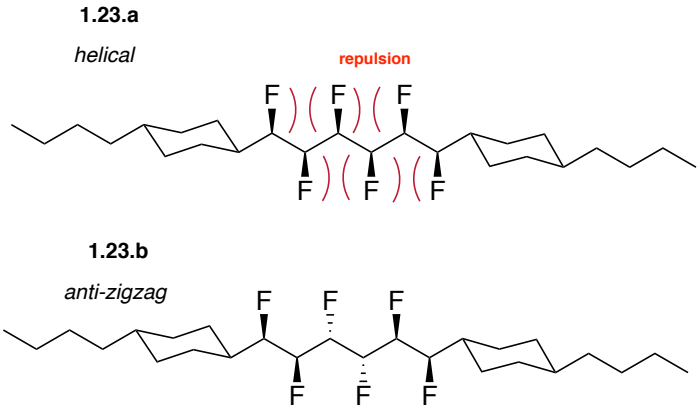
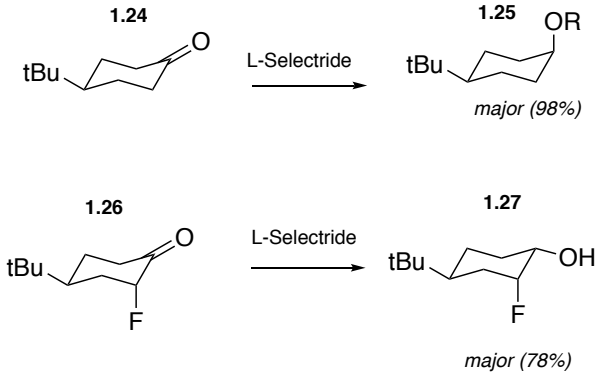


Figure 1.4: Vicinal hexafluorostereoisomers 1.23 and 1.24. *All-syn* 1.23 adops a helical arrangement and 1.24 adopts the a*nti*-zigzag conformation due to the absence of the 1, 3-dipolar repulsions.[35]

1.3.5. Facial selectivity.

When a functional group such as a carbonyl lies adjacent to a CF bond and it is subjected to nucleophilic attack, the trajectory of the nucleophilic addition is very much dictated by the position of the fluorine. The facial preference for nucleophilic attack is found to be *anti* to the C-F bond. This is clearly represented in studies involving the reduction of 2-F-4-tert-

butylcyclohexanone **1.26** with L-Selectride to give a major product **1.27**, which is a complete reversal in diastereoselectivity in comparison to reduction of its non-fluorinated analogue **1.26** (Scheme 1.9).[36,37]



Scheme 1.9: Reduction of 4-tertbutylcyclohexanone 1.24 and 2-F-4-tert-butylcyclohexanone 1.26 with L-Selectride gave product alcohols 1.25 and 1.27.[36, 37]

1.4. Fluorinating reagents.

In the earth's crust the most common flourine-bearing minerals are natural cryolite ($AlF_3.3NaF$), phosphate rock ($Ca_5(PO_4).3F$) and fluorspar, also known as fluorite (CaF_2). Fluorite is mined as a source used to produce hydrofluoric acid (HF). [38]

Equation 1

$$CaF_2 + H_2SO_4 \rightarrow 2HF + CaSO_4$$

HF, which is generated from the reaction of fluorspar with sulphuric acid (eq.1), has several important applications in organic chemistry, including the production of fluorocarbons and the generation of elemental fluorine (F_2). [38,39] Fluorine gas (F_2), which is pale yellow oxidising, toxic gas, is produced through electrolysis of potassium fluoride (KF) in HF, where F_2 is formed at the anode and hydrogen gas is formed at the cathode (eq.2). [38(a),40] It is one of the most energy consuming electrolytic process amongst commercial examples, where pro rata of a fluorine cell is about five times that of cells used in chloroalkali industry.[38(b)]

$$HF + KF \rightarrow KHF_2$$

Equation 2

$$2KHF_2 \rightarrow 2KF + F_2 + H_2$$

1.4.1. Electrophilic fluorinations.

Elemental fluorine (F_2) can be used as an electrophilic source of fluorine for the generation of organofluorine compounds. However, poor selectivity is generally attained and these fluorination procedures require special equipment and air-free, anhydrous conditions in order to handle the toxic and reactive gas. More desirably, selective and easier to handle sources of electrophilic fluorination can be found in a range of electrophilic reagents that are derived from F_2.[40] Electrophilic reagents operate through the transfer of "F^+" to an electron-rich atom and are generally based on F-F, O-F and N-F bonds.

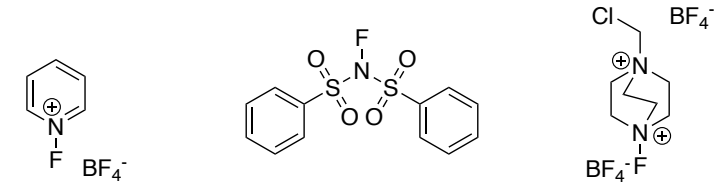
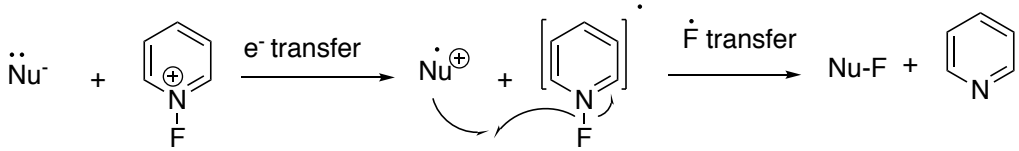


Figure 1.5: Common electrophilic fluorinating reagents.

The lower electronegativity of nitrogen when compared to oxygen results in more stable N-F then O-F species, thus these reagents are easier to handle and as such *N*-Fluoro electrophilic reagents are the more common of this type. The three main classes are: *N*-fluoropyridinium salts, *N*-Fluorosulfonamides and Selectfluor derivatives (see Figure 1.5).



Scheme 1.10: Fluorination with N-fluoropyridinium salts through an electron transfer mechanism. [41]

N-Fluoropyridinium salts, fluorinate nucleophilic substrates through a single electron transfer process (Scheme 1.10) and their reactivity can be tuned through derivatisation of the pyridine heterocycle. *N*-Alkylsulfonamides such as *N*-fluorobenzenesulfonimide (NFSI) (Figure 1.5) were first reported as a class of fluorinating reagents by Barnette *et.al.* in 1984.[41] *N*-Alkylsulfonamides are prepared upon treatment of *N*-alkylsulfonamides with F_2 and can fluorinate a wide range of anions, such as alkyl and aryl organometallics, malonates, ketones and amide enolates. [41]

Selectfluor (Figure 1.5) was developed by Banks *et.al,* and offers an effective source of electrophilic fluorine.[42] Selectrofluor is commercially available and found to be bench stable

and widely used as an electrophilic source of fluorine in organofluorine chemistry. This class of reagents is found to be powerful oxidants, and their reactivity can be enhanced by the substitution of electron-withdrawing groups on nitrogen atom.[43]

1.4.2. Nucleophilic fluorinations and deoxyfluorinations.

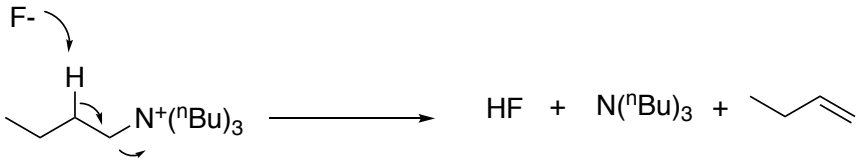
Nucleophilic reagents, in contrast to the electrophilic reagents described above, are dependent on delivering fluoride anion. These reagents can be classified into two groups, either hydrogen fluoride additives or deoxyfluorinating reagents.[40]

Alkali metal fluorides
NaF CsF KF AgF
Tetraalkylammonium fluorides
F^- $N^+(^nBu)_4$ **TBAF**
F^- $N^+(Me)_4$ **TMAF**
HF reagents
(HF)x **Olah's reagent**
3HF
S-F based reagents
DAST
Deoxo-Fluor®
Fluolead™
α-fluoroamine reagents (FAR)
Yarovenko's reagent
Ishikawa's reagent (1:3 ratio)
TFEDMA reagent
C-F based reagent
DFMBA

Table 1.2: Nucleophilic fluorination reagents.

Tetrabutylammonium fluoride (TBAF) and tetramethylammonium fluoride (TMAF) are organic solvent soluble and common reagents where fluoride ion can be used in combination with tetraalkylammonium ions (Table 1.2).

These reagents can be unpredictable due to the occurrence of Hoffman eliminations, whereby fluoride anion abstracts a β-hydrogen promoting an E1cB/ E2 mechanism, illustrated in Scheme 1.11. These reagents are difficult to dry and problems arise with the presence of water, which through hydrogen bonding can lower the nucleophilicity of F^- and this also lead to side reactions, such as hydrolysis.

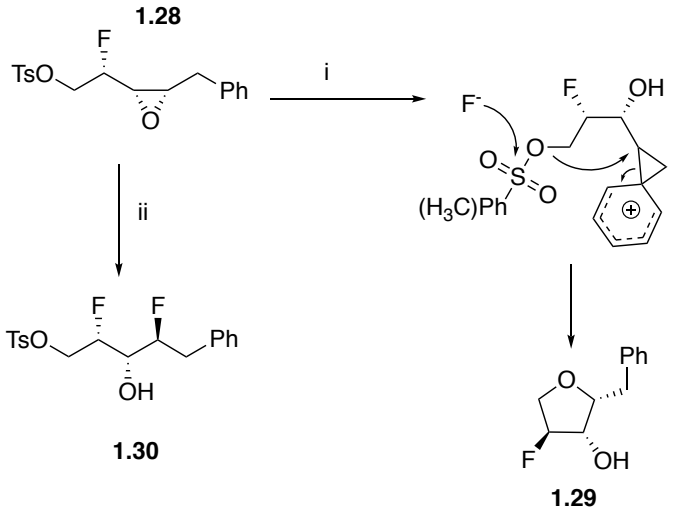


Scheme 1.11: Decomposition of TBAF through Hoffman E2 elimination mechanism.

Unlike F_2, which is a gas, HF has a boiling point of 19.6 °C and when combined with an amine it can form a stable reagent. Two of the most common forms are triethylamine HF ($Et_3N.3HF$) or Pyridine.HF (Py.HF), the latter of which is known as Olah's reagent (Table 1.2). Olah's reagent, first reported in 1973, consists of pyridine (30%) and hydrogen fluoride (70%) and is stable up to 55 °C.[44] In addition to being able to fluorinate a number of electrophiles, it can also add HF across the double bond of an alkene.

In comparison to Olah's reagent, with which reactions can take place at lower temperatures, triethylamine HF is a milder reagent, which consists of 37% HF and 63% of Et_3N. It has a b.p of 70 °C. Despite being less reactive, and often requiring higher temperatures and longer reaction times due to its reduced acidity, these conditions can sometimes benefit certain reactions.

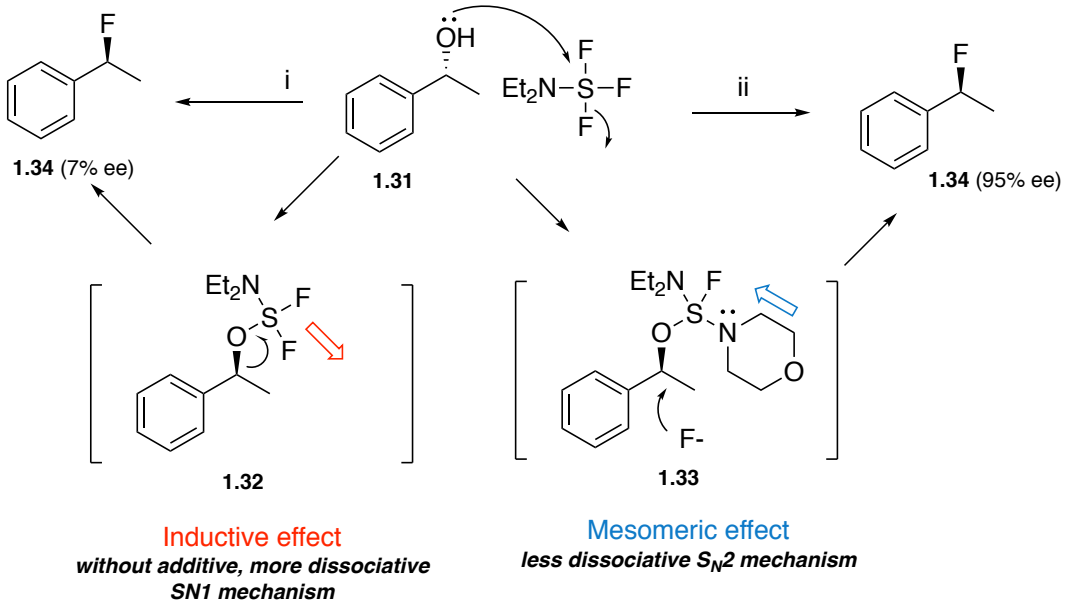
For example during the preparation of vicinal trifluoro motifs, treatment of epoxide (**1.27**)(Scheme 1.12) with acidic Py.HF (70%) lead to tetrahydrofuran **1.29** through protonation of the epoxide followed by a phenonium ion intermediate (**1.28**), while reaction of **1.27** with $Et_3.3HF$ lead to the desired substituted product **1.30** through an S_N2 mechanism (Scheme 1.12).[45] Nevertheless both of these reagents are still not as basic as TBAF or CsF and therefore are less likely to cause elimination reactions.



Scheme 1.12: Reaction of fluoro-α,β-epoxide (1.27) with (i) Pyr.HF (1.29, 33%);(ii) Et_3.3HF, CH_3Cl_3, 100 °C (1.30, 58%).[45]

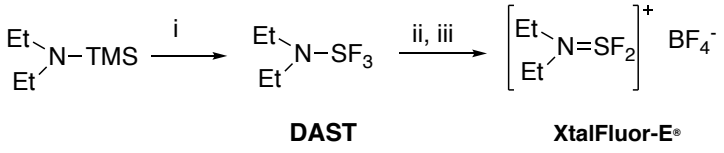
The most widely used class of reagents for deoxyfluorination reactions are S-F based reagents (Table 1.2). The nucleophilicity of fluoride greatly increases due to pairing a soft Lewis acid with a hard Lewis base F^-. DAST (Table 1.2), first reported in 1975 by Middleton *et.al*, was introduced as an alternative to the highly reactive and difficult to handle SF_4 gas.[46] This reagent can convert alcohols into monofluorides, carbonyls to difluorides and carboxylic acids to the trifluoromethyl derivatives.[46–48] DAST is prepared from the combination of diethylaminotrimethylsilane with SF_4 (Scheme 1.14, reaction (i)) and is one of the most widely used reagents for deoxyfluorination reactions, however it has poor stability under heating and is difficult to use on scale.[46] Bis(2-methoxyethyl)aminosulfur trifluoride also known as Deoxo-Fluor® was introduced as an alternative to DAST in 1999 (see Table 1.2).[48] The greater thermostability of this reagent can be justified by its coordination of the ether side chains with the electron-deficient S-atom of the trifluoride. [48]

These reagents operate through nucleophilic attack by fluoride of the *in situ* activated alcohol. In general however, deoxyfluorination reactions with these reagents tend not to be stereoselective due to competing S_N1 type reactions.[49] The addition of TMS-amine to RSF_3 reagents was found to greatly improve the selectivity during deoxyfluorination of enantiomerically pure substrates such as (R)-1-phenylethanol (**1.31**) to form (*S*)-(1-fluoroethyl)benzene (**1.34**) (see Scheme 1.13). The stability lies in the additional nitrogen lone pair derived from the amine, acting as a mesomeric donor in intermediate **1.33**, reducing leaving group propensity and promoting S_N2 versus S_N1-type displacement. This was shown to increase the enantiomeric purity of the product, which otherwise lost their enantiopurity (Scheme 1.13).[49,50]



Scheme 1.13: Stereoselective deoxyfluorination (i) DAST, CH_2Cl_2 (7% ee); (ii) DAST, 4-TMS-morpholine, CH_2Cl_2 (95% ee).[49]

The more recently introduced deoxyfluorinating reagents diethyl aminodifluorosulfinium tetrafluoroborate (XtalFluor-E®) and morpholinodifluorosulfinium tetrafluoroborate (XtalFluor-M®) were introduced in 2009 by Couturier *et.al* (see Table 1.2).[47,51] These tetrafluoroborate salts, are found to be stable and easier to prepare than DAST or Deoxo-Fluor®, which require hazardous distillation of the dialkylaminosulfur trifluorides. XtalFluor-E® is prepared in a one-pot reaction by addition of SF_4 to diethyltrimethylsilylamine, in order to generate DAST, followed by fluoride ion transfer from BF_3.THF resulting in tetrafluoroborate salt (Scheme 1.14).[51,52]

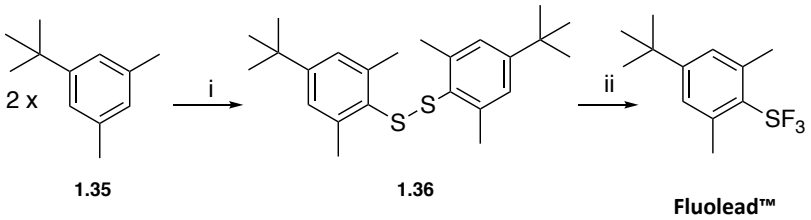


Scheme 1.14: Synthesis of XtalFluor-E®; (i) SF_4, CH_2Cl_2, rt, 16 h; (ii) BF_3.THF, CH_2Cl_2, rt, 1 h; (iii) Filtration (90%).[52]

Primary, secondary, tertiary, and allylic alcohols can be fluorinated with these reagents with higher selectivity and fewer elimination reactions in comparison to DAST and Deoxo-Fluor®.

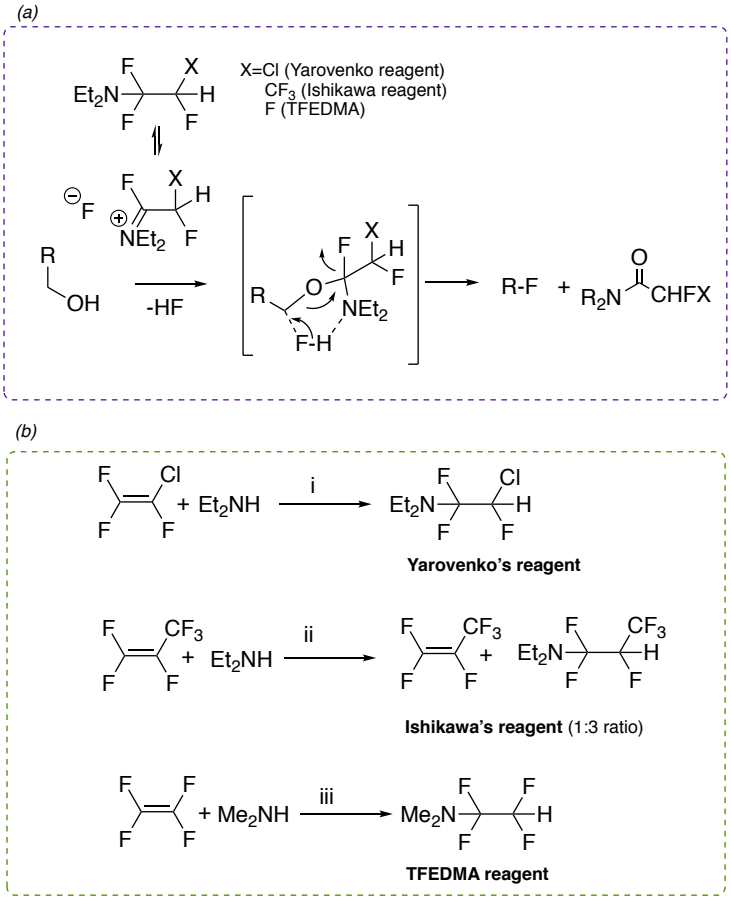
One of the most recently developed reagents in this category is 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead™).[53] Fluolead™ was developed by Umemoto from a first generation phenylsulfurtrifluoride ($PhSF_3$) reagent and was found to be more chemically stable with good reactivity.[53] It is prepared from reaction of 3,5-dimethyltert-butylbenzene (**1.35**) and sulphur monochloride in the presence of catalytic amounts of $ZnCl_2$

to form diaryl disulfides (**1.36**), which is then reacted with chlorine and KF to furnish Fluolead™ (Scheme 1.15).[53]



Scheme 1.15: Preparation of Fluolead™; i) S_2Cl_2, $ZnCl_2$(cat.), AcOH, rt, 4 h (1.42, 79%); ii) Cl_2, KF, MeCN, 0 °C to rt (82%).[53]

In comparison to DAST, Fluolead was found to be much more stable to water and heat. [53] The key success of Fluolead™ lies in its design, where the substitution on the aryl ring greatly increases its reactivity and stability due to the C-S bond, which is much stronger than the N-S bond of DAST (714 kJ mol^{-1} vs 464 kJ mol^{-1}).[53]



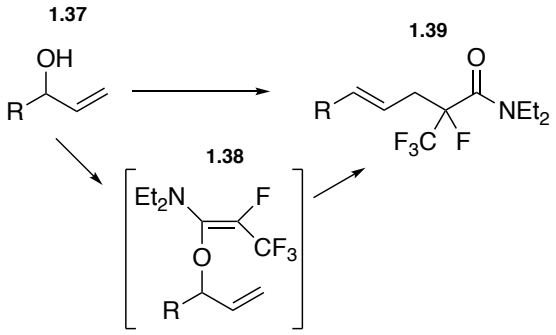
Scheme 1.16: (a) General mechanism for alcohol deoxyfluorination by FARs; (b) Synthesis of FAR reagents; (i) CH_2Cl_2, –20 °C to 5 °C (Yarovenko's reagent, 80–90%); (ii) EtO, -70 °C to rt, overnight (72%, Ishikawa's reagent); (iii) neat, 0-5 °C (TFEDMA reagent, 96–98%).[54-56]

Even though this reagent is fairly new and not yet widely used, it is already shown to

fluorinate a wide range of substrates including alcohols, aldehydes, enolizable ketones to form C-F bonds and CF_2 groups, carboxylic groups to CF_3 and ROC(=S)SCH_3 to $ROCF_3$.[53]

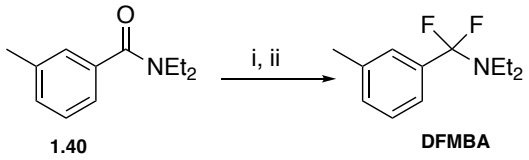
Another class of deoxyfluorinating reagents is derived from a combination of diethyl amine and a corresponding fluoro olefin to form α-fluoroamines (also known as FARs) (Scheme 1.16). FARs can convert primary and secondary alcohols into alkyl fluorides as shown on Scheme 1.16 (a).[54a,b] The first of this class was reported in 1959, by Yarovenko and Raksha from Et_2NH and chlorotrifluoroethene (Scheme 1.16 (b), i).[54b] Ishikawa's reagent was reported in 1979 as an adduct of perfluoropropene–diethylamine (PPDA), (Scheme 1.16 (b), ii).[55]

The most recent reagent of this class is prepared from tetrafluoroethylene and dimethylamine to form 1,1,2,2-tetrafluoroethyl-N, N-dimethylamine (TFEDMA) (Scheme 1.16 (b), iii).[56] In contrast to similar reagents, TFEDMA is cheaper to produce due to the low price of tetrafluoroethylene.[56] A limitation is the formation of side products through dialkyl ether intermediates formed by a Claisen 3,3-sigmatropic rearrangement (Scheme 1.17, intermediate **1.38**) when allylic and propargylic alcohols are used.[57]



Scheme 1.17: Side product formation of FAR reagents; PPDA (2.0 equiv); $(i\text{-}Pr)_2NEt$ (2.0 equiv), $CHCl_3$, rt.[57]

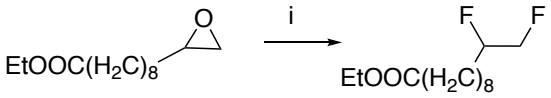
N,N-Diethyl-α,α-difluoro(meta-methylbenzyl)amine (DFMBA) is another noteworthy deoxyflurinating reagent. It was first reported in 2004 by Hara *et.al.,* where DFMBA was obtained by chlorination of N,N-diethyl-3-methylbenzamide (**1.40)** with oxalyl chloride, followed by fluorination with triethylamine HF (Scheme 1.18).[58]



1.40 **DFMBA**

Scheme 1.18: Preparation of DFMBA ; (i) $COCl_2$, CH_2Cl_2, reflux, 24 h; (ii) $Et_3N.3HF$, Et_3N (84%).[58]

It is able to fluorinate a wide range of substrates including primary, secondary and benzylic alcohols to fluorides, aldehydes to gem-difluorides, 1, 2- and 1,3- diols to acylated fluorohydrins as well as β-diketones to β-fluoro-α,β-unsaturated ketones. One of the more remarkable fluorinations demonstrated by DFMBA was the conversion of epoxide (**1.41**) to vicinal-difluoride (**1.42**), which had previously been found to be difficult to generate (Scheme 1.19). [59]

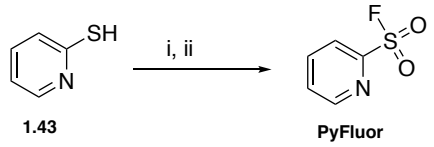


1.41 **1.42**

Scheme 1.19: i) DFMBA (1.5 equiv), $Et_3N.3HF$ (0.5 equiv), 180 °C, 30 min, (78%).[59]

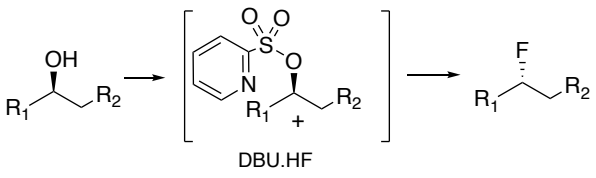
A last but not least, a relatively new yet selective deoxyfluorination reagent worth mentioning is PyFluor (Scheme 1.20). Reported in 2015 by Doyle *et al.*, PyFluor showed to be stable against elimination reactions and mild alternative to current popular deoxyfluorinating reagents such as Deoxo-Fluor® or DAST.[60]

(a)



1.43 **PyFluor**

(b)

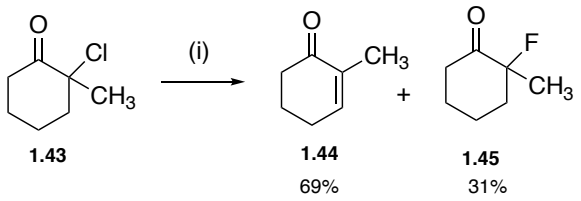


DBU.HF

Scheme 1.20: (a) Preparation of PyFluor: i) 13% NaOCl (slow addition), H_2SO_4, 0 °C, 4 h; ii) sat. KHF_2:CH_3CN, rt, 20 min (73%); (b) General fluorination of secondary alcohol with PyFluor. [60]

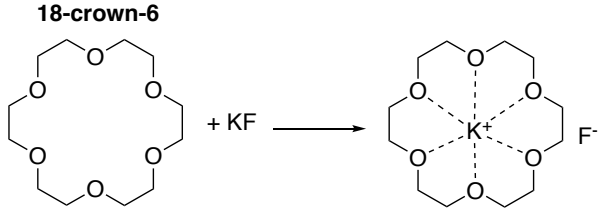
It is also found to be inexpensive and prepared from oxidation of 2-mercaptopyridine (**1.43**) with aqueous sodium hypochlorite to form 2-pyridinesulfonyl chloride followed by treatment with potassium bifluoride resulting in PyFluor (Scheme 1.20 (a)). The drawbacks of this reagent are longer reaction times and the requirement of using strong bases such as TBBD and DBU. The suggested fluorination mechanism for PyFluor with secondary alcohol is shown on Scheme 1.20 (b).[60]

Alkali-metal fluoride salts such as KF and CsF are a popular source of nucleophilic fluoride ion due to their low cost (Table 1.2). However, there are several problems associated with those reagents due to their poor solubility in organic solvents and elimination side reactions, which arise due to the basicity of 'naked' fluoride ion.[60,61] Primary halides generally behave well, however with secondary halides, fluoride ion acts as a base and elimination becomes the dominant process.[61] A competition between fluoride ion acting as a nucleophile or a base is illustrated in the reaction of the tertiary chloride (**1.43**) with KF, where the elimination product **1.44** dominates over **1.45**, as shown in Scheme 1.21.[61]



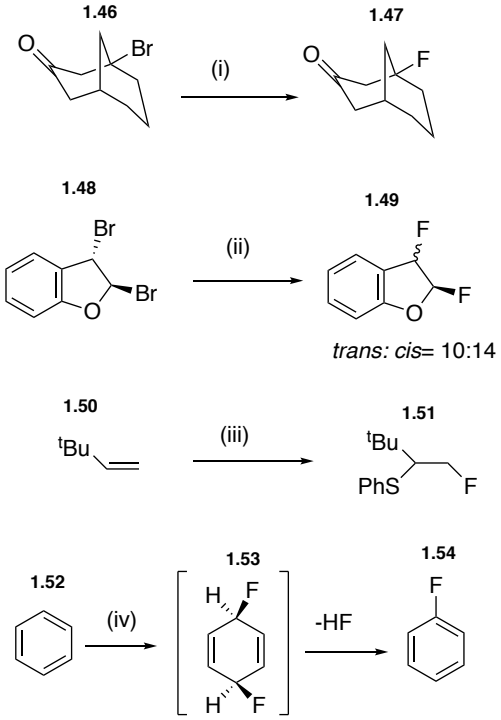
Scheme 1.21: KF, 18-Crown-6 ether (cat. amount), MeCN, 83°C, 20 h (The time for one-half conversion of starting materials to products), 1.44 (69%), 1.45 (31%).[61]

In order to increase the solubility and hence their reactivity, alkali metal fluorides are often used along with crown ethers.[40,43] In studies by Liotta *et.al* it has been shown that 18-crown-6 is an effective agent to dissolves metal salts by forming KF-crown ether complex (Scheme 1.22) in aprotic, polar and non-polar solvents.[60,61]



Scheme 1.22 Formation of the KF-18-crown-6 ether complex. [40,43]

Silver(I) & (II) fluorides (AgF & AgF_2), are other popular sources of alkali-metal fluorides. Both of the reagents are found to be light sensitive and hygroscopic. AgF is often used to fluorinate alkyl and aryl halides under mild conditions (Scheme 1.23, reaction (i)).[62] For example it has been used to fluorinate *trans*-2,3-dibromo-2,3-dihydrobenzofuran to generate *cis*- and *trans*-2,3-difluoro-2,3-dihydrobenzofuran (**1.49**) (Scheme 1.23, reaction (ii)) as well fluorinate electron deficient alkenes.



Scheme 1.23: Fluorination reactions using AgF; (i) AgF, Pentane, dark, 1.56 (83%); (ii) AgF, benzene, MeCN, 0 °C, 5 h 1.58 (*trans: cis*= 10:14) (60%); (iii) AgF, PhSCl; MeCN, 1.60 (70%); (iv) AgF_2, n-hexane, reflux, 1.62 (61%).[62,63]

When sulfenyl chloride along with AgF is added to the reaction with an alkene (**1.50**), β-fluoro thioether **1.51** was produced as a result of an anti-Markovnikov addition.[62] AgF_2 is also used in the fluorination of alkyl halides and aromatic compounds, where it acts as a strong nucleophilic fluoride source and oxidant.

Treatment of benzene with AgF_2 generated fluorobenzene (**1.54**) in good yield (Scheme 1.23, reaction (iv)).[63] Monofluorinated product is obtained through 1,4-electrophilic addition of two fluorine atoms, followed by HF elimination, resulting in **1.54** (Scheme 1.23). [63]

1.5. Applications of organofluorine compounds in medicinal and agrochemical chemistry.

Fluorinated organic compounds have made an impact in agrochemical and medicinal chemistry, accounting for 20% of all the drugs in pharmaceutical market in 2010, which has risen to 30% since then.[3,64,65] The first fluorinated pharmaceutical drug on the market was fludrocortisone, reported in 1954. In 1955 this *anti*-inflammatory steroid (corticosteroid), which was a primary drug of this class, was approved by the U.S. Food and Drug Administration (FDA). [65,66] Since the launch of fludrocortisone, there has been nearly 150 fluorinated compounds introduced to the pharmaceutical market.[65]

These include the biggest selling drugs in 2016, such as Rucaparib (**1.55**) (treatment for women with ovarian cancer), Sofosbuvir (**1.56**) (hepatitis C treatment), Fluciclovine F^{18} (**1.58)** used as a PET imaging agent for prostate cancer and Pimavanserin (**1.57**) used for treatment of hallucinations (Figure 1.6). In 2017, six drugs out of the 39 approved by the FDA contained at least one fluorine atom.[67]

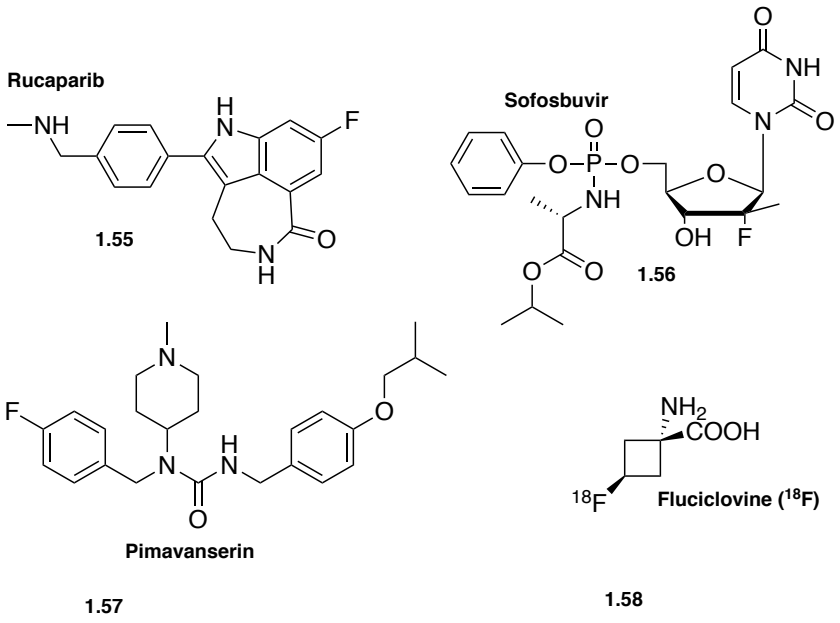
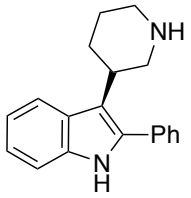


Figure 1.6: FDA Novel Drug Approvals for 2016; Rucaparib, Fluciclovine ^{18}F, Pimavanserin.

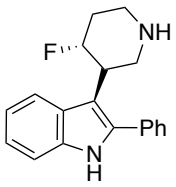
In order for new chemical entities (NCEs) to be effective drug candidates, several key factors have to be considered. These including, biological activity, efficacy of administration, metabolism and the toxicity of the target compound in humans. Introduction of fluorine into a drug candidate can play a key role in adjusting those features.[3,4,65]

1.5.1. pK_a effect.

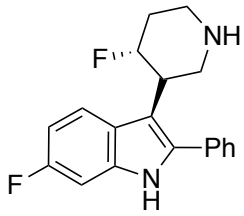
The substitution of fluorine into bioactive compounds can influence the acidity or basicity of the adjacent functional groups. As a consequence, this will affect the binding affinities and the pharmacokinetic properties of a drug candidate as well as its absorption in orally administered drugs.[2,64]



1.59



1.60



1.61

	1.59	**1.60**	**1.61**
[(i)] $5HT_{2A}$	0.99	0.43	0.06
[(ii)] pK_a	10.4	8.5	-
[(iii)] F (%)	0.06	18	80

Table 1.3: (i) Affinities at human cloned $5HT_{2A}$; (ii) pK_a; (iii) F(%), Bioavailability calculated from dosing at 0.5-2 mg/kg intravenous and orally.[68]

During studies conducted by Rowley *et.al* on 3-piperidinylindole antipsychotic drugs, a key development was the discovery of a bioavailable and selective Serotonin 5-HT_{2A} receptor antagonist that did not carry side effects associated with affinity to the IKr potassium ion channel.[68] Introducing the fluorine on the piperidine ring reduced the pKa of the basic nitrogen from 10.4 (non-fluorinated compound **1.59**) to 8.5 (3-(4-fluoropiperidin-3-yl)-2-phenyl-1H –indole, **1.60**), which consequently improved its oral bioavalibility up to 18 % (Table 1.3). The compound was also found to be more selective to 5-HT_{2A} receptor binding and with only a small affinity to IKr. In addition to pK_a modifications, the studies also showed that fluorine blocks oxidation at the 6-position of the indole ring, and increased its bioavalability by up to 80% and its half-life to 12 h.[68]

1.5.2. Lipophilicity.

Lipophilicity is a physicochemical property related to the ability of a compound to dissolve in fats and lipophilic non-polar solvents. The hydrophobic constant, log P, is derived from the measurement of the partition coefficient between the two opposing phases such as water and octanol, with polar hydrophobic compounds moving to the water layer and less polar hydrophilic compounds to the octanol layer.[4,69] By altering the polarity of a candidate drug, it is possible to obtain the desired lipophilicity for *in vivo* adsorption, directly related to the solubility, absorption, distribution and penetration into the brain as well as other body organs. For orally administered drugs, passive transport is the main form of drug distribution. Passive transport is reliant on membrane permeability, therefore drugs have to be lipophilic enough to be able to pass through the cell membrane, but not overly lipophilic that they will 'stick' in the membrane. Following the Lipinski 'rule of five', in order for an orally administered drug to have 'good' permeability, the calculated Log P, should not be higher than 5 and ideally in the 1-3 range.[70] Poor absorption is a common problem in drug development, which often arises due to high lipophilicity and fluorine substitution can play an important role. It is important to recognise that insertion of fluorine into an organic molecule, can either increase or lower the lipophilicity, depending on the location of the substitution.[6] For example introduction of poly and per-fluorinated motifs eg. CF_3, will generally increase the lipophilicity of the molecule .[4,6]

In contrast to this, mono-, di- and trifluorination of saturated alkyl groups, can lower the lipophilicity of the compound due to polarisation of the adjacent C-H bonds. Muller *et.al*, highlighted that lipophilicity decreases on introduction of fluorine into *n*-propylbenzene derivatives (Table 1.4). Fluoromethyl and difluoromethyl derivatives **1.63** and **1.64**, are more polar then the parent alkyl group and even the trifluoro derivative is less lipophilic. [71,72]

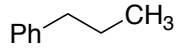
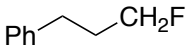
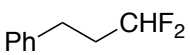
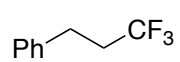
		Log P
1.62		3.7
1.63		3.0
1.64		3.1
1.65		3.3

Table 1.4: Lipophilicities of partially fluorinated *n*-propylbenzene derivatives .

1.5.4. Fluorine effects on Metabolism.

Oxidative metabolism.

Cytochrome P450 monooxygenases hydroxylate drugs and xenobiotics *in vivo*. These enzymes are mainly found in liver cells and account for 75 % of the total metabolism of drugs.[73] When P450 monooxygenases metabolise a drug through oxidation, it alters its lipophilicity allowing more rapid excretion. Often low metabolic stability and quick clearance is a problem leading to low efficacy. In order to overcome this problem fluorine can be introduced to block oxidation sites.[3,4,64]

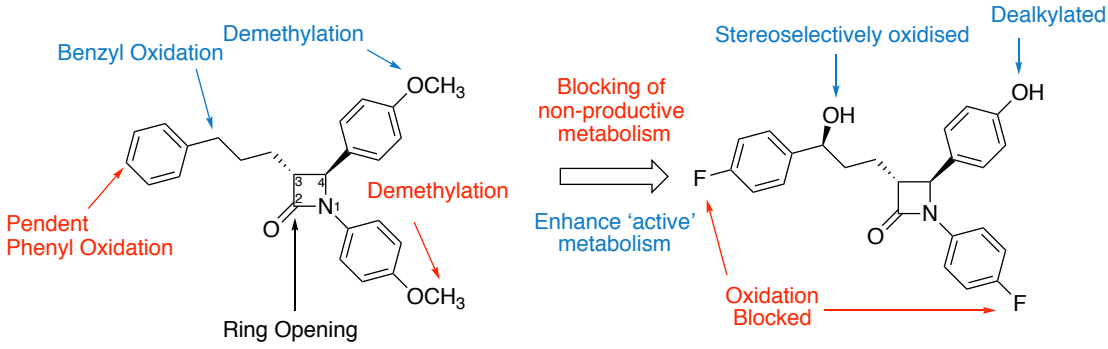
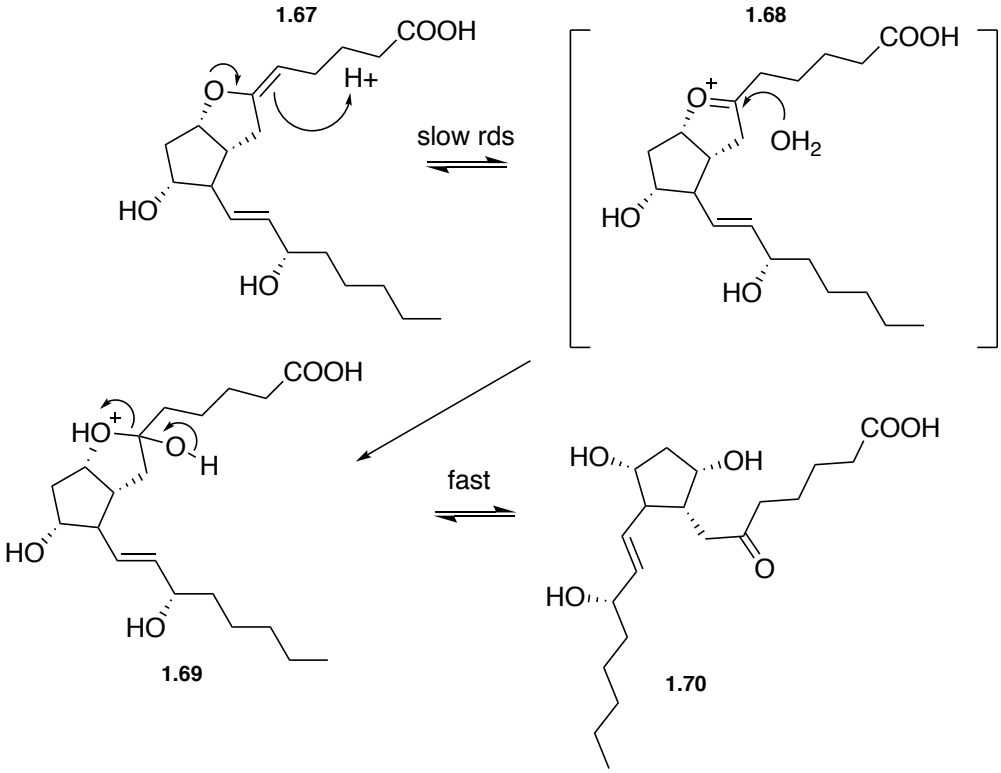


Figure 1.7: Lead optimization studies of Ezetimib.[74]

One such example in the selective cholesterol-absorption inhibitor, Ezetimib (Figure 1.7).[74] Through metabolite structure-activity relationship (SAR) analyses of the first lead compound (**1.66**), five primary metabolism sites were recognized with more than 40 potential metabolites expected (Figure 1.7). Introduction of fluorine atoms at the para-positions of the phenyl rings resulted in blocking metabolism and resulting in a 50-fold potency increase when compared to the original lead compound.[74]

Hydrolytic metabolism.

Hydrolytic stability is important in drug metabolism, as certain biologically active compounds are easily hydrolysed and this results in a shorter half-life. Strategic introduction of fluorine at certain positions can suppress hydrolysis. [4] Prostacyclin (**1.67)**, (PGI_2), is a hormone that inhibit blood platelet aggregation, however it also undergoes facile hydrolysis to form 6-keto-$PGF_{1\alpha}$ (**1.70**), with a half life of only 10 minutes (Scheme 1.24).[4,75]



Scheme 1.24: Hydrolysis mechanism of prostacyclin to form 6-keto-$PGF_{1\alpha}$.[4,75]

The mono-fluorinated analogue (**1.71**) of PGI_2, has a half life (at pH 7.4) of 1 month by comparison, as fluorine withdraws electron density from the enol ether and suppresses the formation of the intermediate oxocarbenium ion and thus slows hydrolysis (see Figure 1.8).[76]

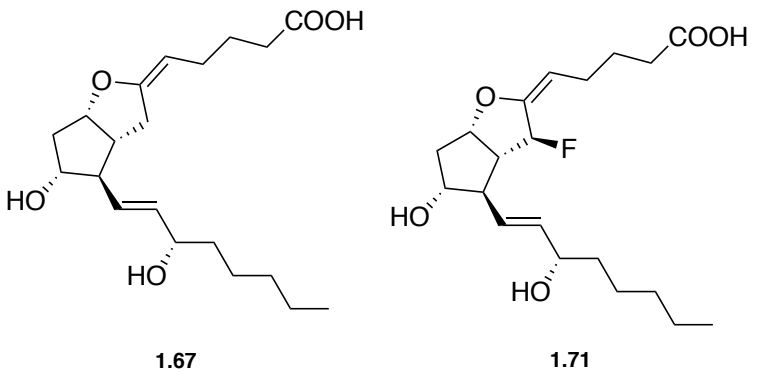
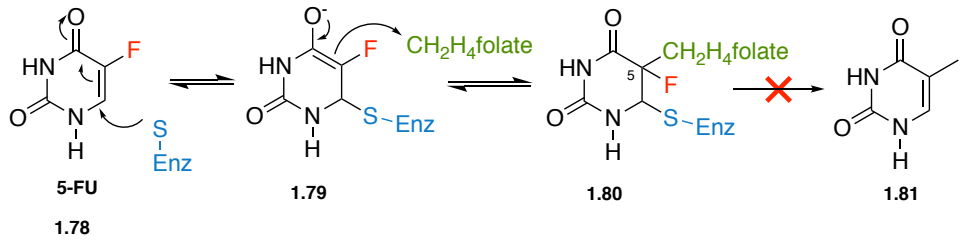


Figure 1.8: Prostacyclin with half life of 10 minutes at pH 7.4 and (7S)-7-fluoro-PGI_2 analogue with half life of 1 month at pH 7.4.[76]

1.5.5.The role of fluorine in mechanism based inhibitors.

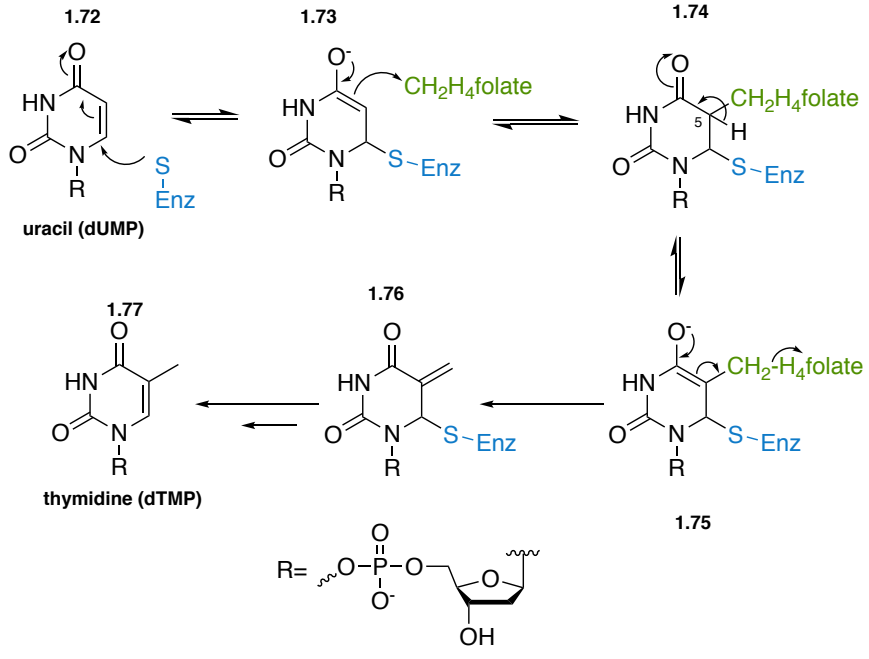
Fluorine has a limited steric influence, however its electrostatic properties can change the pathway of metabolic mechanisms. One such example is represented by 5-fluorouracil (5-FU) (Scheme 1.25), a widely used anticancer drug.



Scheme 1.25: Fluorocil (5-FU) mechanism of thymidylate synthase (TS) inhibition.[4]

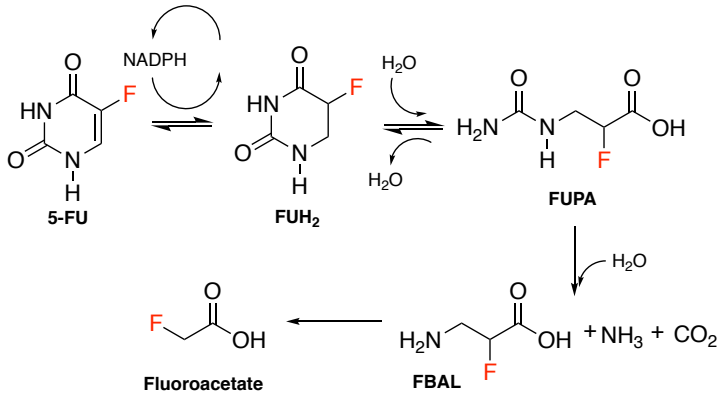
5-Fluorouracil was first reported in 1957, and is still one of the main treatments against a wide range of cancerous tumours.[79] It operates through competitive binding to thymidylate synthase (TS), an enzyme that produces essential precursors for DNA biosynthesis.[77]

In nucleotide biosynthesis, TS is responsible for the conversion of deoxyuridine monophosphate (dUMP) (**1.72**) to deoxythymidine monophosphate (dTMP) (**1.77**). The first step in the mechanism involves the Michael addition of an active site cysteine to dUMP, followed by nucleophilic attack of dUMP (C-5) on co-factor. This then leads to elimination of thymidine (Scheme 1.26).[77,78]



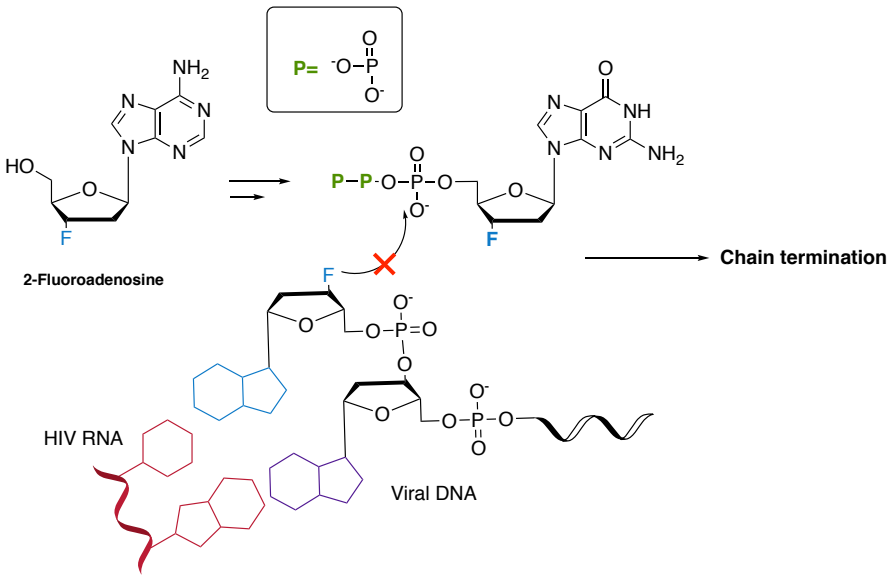
Scheme 1.26: Mechanism of dUPM metabolism.[77,78]

With all inhibiting benefits, which make 5-FU one of the most widely used anticancerous agents, unfortunately the drug carries quite serious neurotoxic and cardiotoxic side effects. After 5-FU is administed intraveniously, more then 80 % is presumed to undergo metabolic degradation resulting in fluoroacetate, which was found to be highly toxic (Scheme 1.27).[79]



Scheme 1.27: Metabolic degradation of 5-FU into toxic fluoroacetate .[79]

Mechanism based inhibition of DNA biosynthesis is an also extremely important for reverse transcriptase inhibition for treatments against HIV. In this case the replacement of the OH for F results in DNA chain termination as illustrated in Scheme 1.28.[80,81]

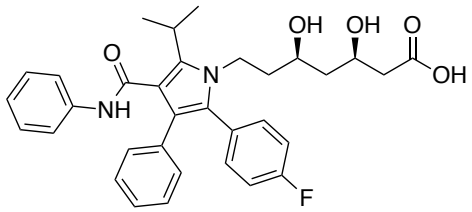


Scheme 1.28: Mode of action of HIV reverse transcriptase fluorinated inhibitor 2-Fluoroadenosine (1.99).

1.5.6. Fluorinated blockbuster pharmaceuticals.

Atorvastatin

Atorvastatin (Lipitor®) is a member of the statin class of drugs, which are used to treat cardiovascular disease by lowering low-density lipoprotein (LDL) cholesterol levels (Figure 1.9). Atorvastatin, acts by mimicking (*R*)-mevalonic acid and competitively binding to the 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), an enzyme involved in cholesterol biosynthesis on the mevalonate pathway.[3,82,83]



Atorvastatin

Figure 1.9: HMG-CoA reductase inhibitor.

Fluoxetine

Fluoxetine (Prozac®) first reported in 1974 by Lilly Research Laboratories and was approved in 1987 by the FDA in US. It became the most administered antidepressant around the world (see Figure 1.10).[84] Although the exact mode of action of serotonin is unclear, it has been shown that inhibiting 5-HT reuptake or metabolism produces positive pharmacological effects.[85]

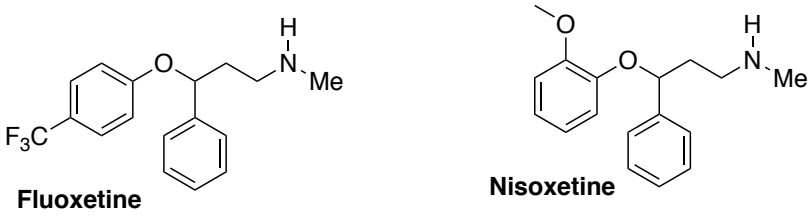


Figure 1.10: SSRI inhibitor Fluoxetine and a similar core structure norepinephrine reuptake inhibitor Neoxatine.[86]

When compared to similar core structures, such as Neoxatine**,** the specificity of Fluoxetine lies in the trifluoromethyl group. This causes the aromatic ring to rotate into a favorable conformation consequently increasing its affinity as a selective serotonin reuptake inhibitor (SSRI), (Figure 1.10).[86]

1.5.7. ^{18}F Positron emission tomography (PET).

Positron emission tomography (PET) using F^{18} is developing very rapidly in the clinical imaging sector, mainly due to a longer half-life of ^{18}F ($t_{1/2}$=109.8 min) in comparison to other radionucleotides such as ^{11}C ($t_{1/2}$=20 min), ^{13}N ($t_{1/2}$=10 min), ^{15}O ($t_{1/2}$=2 min). This allows investigation of metabolic pathways and biodistribution studies of new drugs and drug occupancy studies.[4,87] 2-Deoxy-2-^{18}F-fluoro- β -D-glucose (^{18}F-FDG) being a fluorinated analogue of glucose, it is the most commonly used among fluorinated PET labelling compounds (Figure 1.11). Due to substitution of the OH group at C-2 position by ^{18}F, the compound cannot undergo glycolysis. It gets phosphorylated at O-6 and remains stuck in the cells until the ^{18}F isotope decays into ^{18}O, to become glucose-6-phosphate. This tracer is particularly useful in oncology for tumour detection as cancer cells use glucose at an increased rate.[87]

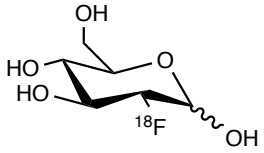


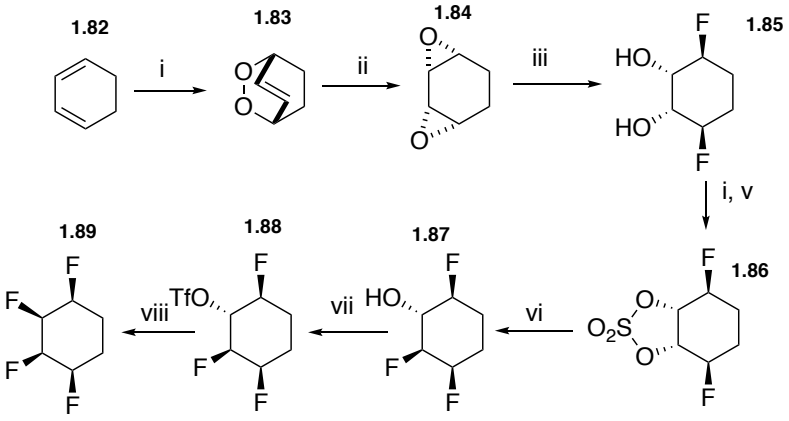
Figure 1.11: 2-deoxy-2-^{18}F-fluoro-β-D-glucose (^{18}F-FDG).

1.6. Previous research: All-*cis*-fluorinated cyclohexane motifs.

This section reviews the previous relevant work in the St Andrews group as a foundation to the work described in this Thesis.

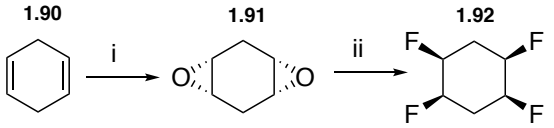
To enhance the polarity of the cyclohexane motifs, it became attractive to synthesize *all-syn* fluorinated cyclohexane rings. In such a structure, the chair conformation forces the fluorine atoms to one face of the ring. Until that point, selectively fluorinated cyclohexane motifs were rare, with only mono- or di-fluorinated cyclohexanes reported in the literature. [88]

The first 1,2,3,4-all-*syn*-tetrafluorocyclohexane motif was synthesised in an 8-step route as shown of Scheme 1.29. The key synthetic feature involved the formation of diepoxide (**1.84**), which was taken through a cascade of fluorination intermediates such as cyclic sulfate (**1.86**) and trifluoro triflate (**1.88**) (Scheme 1.29). The all-*syn* conformation of the final cyclohexane **1.89** forces a 1,3-diaxial fluorine-fluorine interaction when the cyclohexane is in the chair conformation. The co-alignment of two C-F bonds induces a high molecular dipole (4.91 Dy). [89]



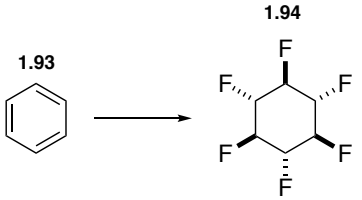
Scheme 1.29: Synthesis of 1.110; (i) $(PhO)_3P$, O_3, CH_2Cl_2, -78 °C then 2, CH_2Cl_2, -78 °C -> -25 °C; (ii) $Ru(PPh_3)_3Cl_2$, CH_2Cl_2, 0 °C->RT, 46%; from 2 steps; (iii) $Et_3N.3HF$, 90 °C; (iv) Thionyl chloride, pyridine, CH_2Cl_2, 0°C; (v) $NaIO_4$, $RuCl_3.xH_2O$, MeCN, H_2O, 35% from 3 steps; (vi) $Et_3N.3HF$, 120 °C, 70%; (vii) Tf_2O, pyridine, RT; (viii) $Et_3N.3HF$, 120 °C, 35% over 2 steps. [89]

All-*syn*-1,2,4,5-tetrafluorocyclohexane (**1.92**) was subsequently prepared through a two-step synthesis (Scheme 1.30).[90] It has even higher polarity than **1.89**, with a calculated molecular dipole of 5.24 Dy.[90]



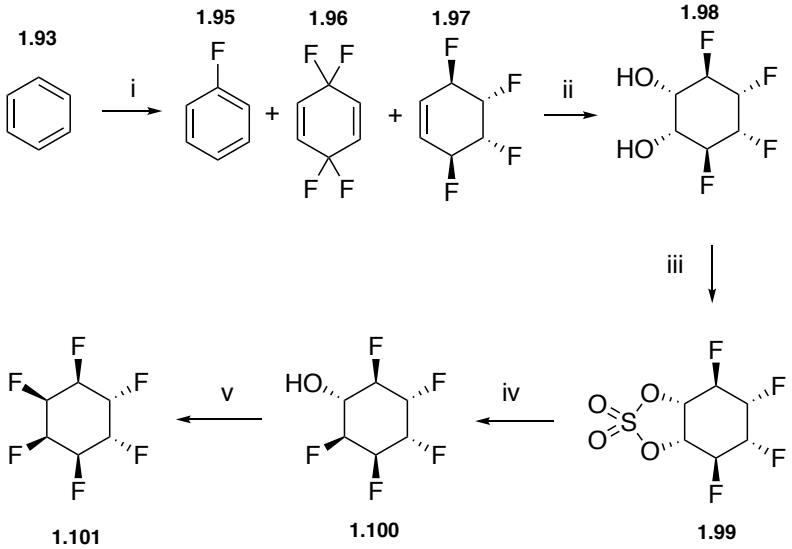
Scheme 1.30: Synthesis of all-*syn*-1,2,4,5-tetrafluorocyclohexane; (i) *m*CPBA, CH_2Cl_2, -15 °C to -10 °C, 52%; (ii) DAST, 70 °C, 24%.[90]

It became an attractive objective to prepare the hexafluorocyclohexane (HFCH) derivatives.[88] Only one report suggesting the possible synthesis of hexafluororcyclohexane had been reported. This involved treating benzene with $KCoF_3$ complex to furnish HFCH (Scheme 1.31).[88] The stereochemistry suggested at the time proposed that the fluorine atoms were all all *trans* in relation to each other, however it was not confirmed and a hexafluorocyclohexane (**1.94**) structure was proposed on the basis of only analytical and empirical data.[88]



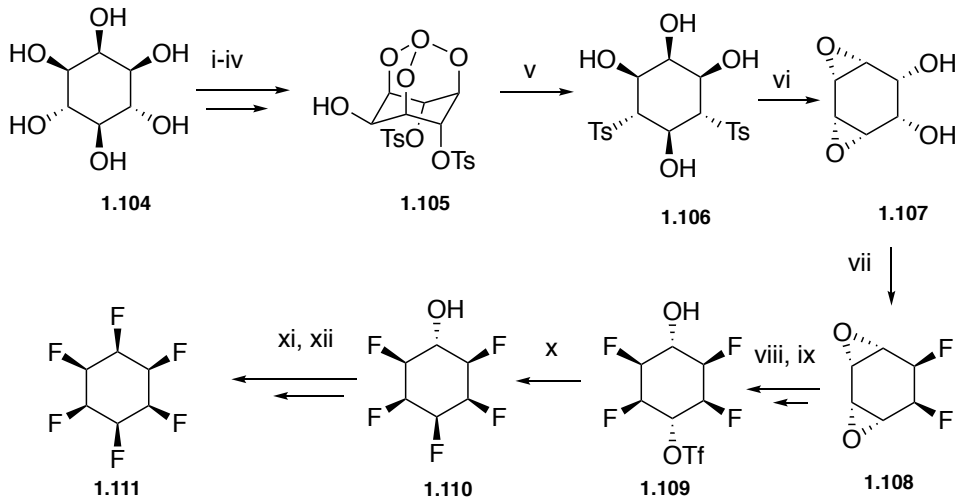
Scheme 1.31: Fluorination of benzene: Potassium cobaltfluoride, flow, 280 °C, 2.5 h, 0.5 %.

The first unambiguous synthesis of a η-1, 2, 3, 4, 5, 6 -hexafluorocyclohexane (**1.101**) was reported from St Andrews in 2012.[91] As shown on Scheme 1.32, it was also prepared from benzene in a 5-step route and as a single stereoisomer. Its stereochemistry has been confirmed by means of X-ray analysis, with four fluorine atoms facing up and two down.



Scheme 1.32: AgF_2, CH_2Cl_2, RT; b) $KMnO_4$, $MgSO_4$, EtOAc, EtOH, H_2O, 0 °C to RT; c) SO_2Cl_2, Et_3N, EtOAc, 2.3% from 3 steps; d) $Et_3N{\cdot}3HF$, 120 °C, 86%; e) Deoxofluor, THF, 55%.

A synthesis of all-*syn*-hexafluorocyclohexane followed because it was predicted to be the most polar of all possible isomers. According to Zdravkovski *et.al.* this is the highest energy stereoisomer of the nine configurational isomers and thirteen conformational isomers. [92] The polarity is arises due to the three axial C-F bonds however, it was uncertain if the synthesis of such a stereoisomer was possible because of the potential for elimination reactions, which may be preferable during the synthesis to overcome these steric and electronic repulsions.[93] However in 2015, all-*cis*-hexafluorocyclohexane (**1.111**) was prepared in St Andrews in a 12 step route, starting from myo-inositol **1.104**, as shown in Scheme 1.33.[93]

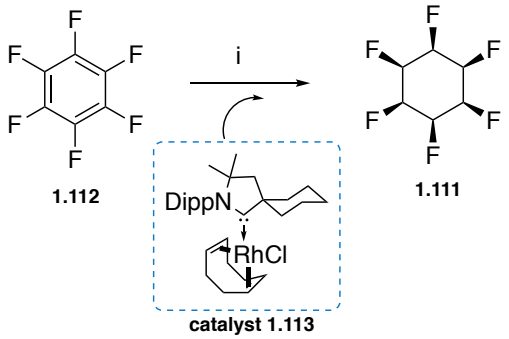


Scheme 1.33: Synthesis of all-*cis*-1,2,3,4,5,6-hexafluorocyclohexane; i) $HC(OEt)_3$, pTSA, DMF, 5 days, 100 ˚C, 69%; ii) NaH, BzCl, DMF, 30 min 55%; iii) TsCl, pyridine, 18 h, 97%; iv) $^{i}BuNH_2$, MeOH, reflux, 4 h, 84%; v) HCl, MeOH reflux, 4 h, 89%; NaOMe, MeOH, $CHCl_3$, 18 h, 85%; vi) Deoxofluor, THF, 60–100 ˚C, 15 min, MW, 94%; vii) Et_3N. 3HF, 180 ˚C, 120 min, MW, 71%; viii) Tf_2O, pyridine, CH_2Cl_2, 88%; ix) Et_3N. 3HF, 120 ˚C, 120 min, MW, 40%; x) Tf_2O, pyridine, CH_2Cl_2, 71%; Et_3N.3HF, 120 ˚C, 120 min, MW, 10%.[93]

Interestingly it has been noted from the X-ray analysis of all-*cis*-hexafluorocyclohexane **1.111**, that the triaxial F-atoms are 2.77 Å from each other, a longer distance than the adjacent F_{ax}-F_{eq} distances (2.73 Å), suggesting increased repulsion between the axial and equatorial fluorine atoms, a repulsive force which acts to stabilise the chair conformation. These fluorinated cyclohexane motifs, are unique due their 'Janus-like' facial polarity and they present a novel motif in organic chemistry.

In an exciting development by Glorious *et.al*, they have shown in 2017 that all-*cis*-hexafluorocyclohexane (**1.111**) can be prepared in a one-step procedure by direct hydrogenation of hexafluorobenzene. This remarkable approach uses a homogeneous ruthenium–N-heterocyclic carbene (NHC) catalyst (**1.113**) and results in complete

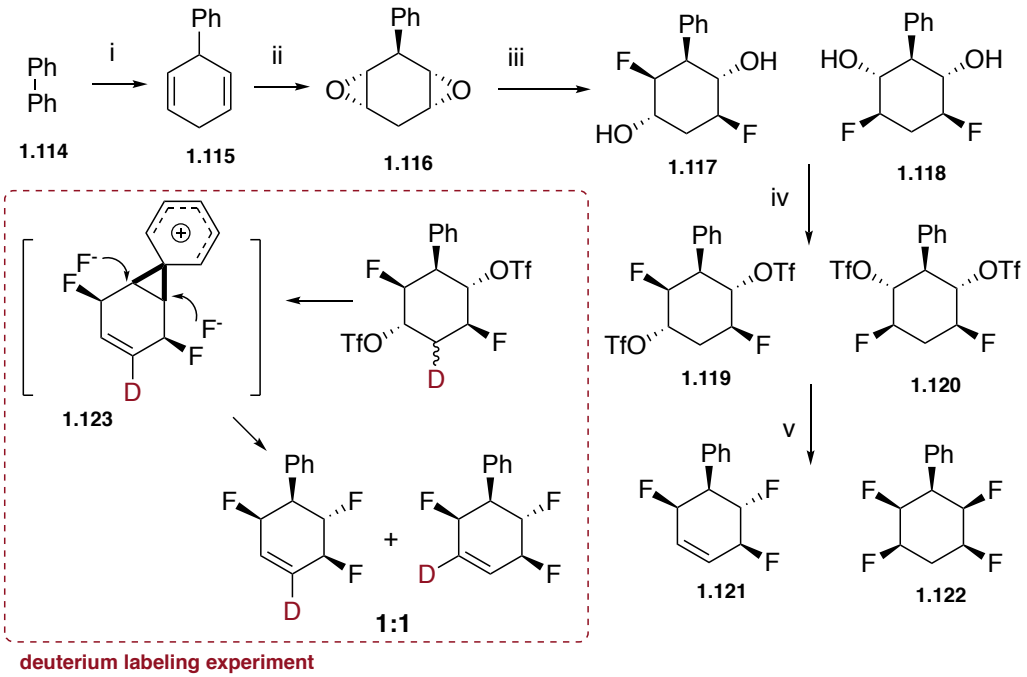
stereoselective hydrogenation (Scheme 1.34).[94] The reduction has also been applied to a range of readily accessible fluorinated arenes such as tetrafluoro cyclohexane **1.95**, generating highly polar fluorinated cyclohexanes in good to excellent yields and selectivities.[94]



Scheme 1.34: Single step synthesis of all-*cis*-1,2,3,4,5,6-hexafluorocyclohexane through catalytic hydrogenation of fluorobenzene; Rhodium-CAAC-COD-Cl, hexane, H_2, 25 °C for 24 h, 34%.[94]

The first analogue of the all-*cis*-fluorinated motif to be prepared by St Andrews group was the phenyl derivative (**1.122**), where the aryl group has served as a foundation for creating a range of these fluorinated cyclohexanes as building blocks.[95] The synthesis to **1.122** consists of 5 steps, starting from a Birch reduction of biphenyl**,** followed by diepoxidation to **1.116** (Scheme 1.35). Diepoxide **1.116** is then fluorinated using triethylamine HF, resulting in the formation of two fluorohydrin isomers. They are converted together into their corresponding triflates, **1.119** and **1.120**. Finally fluorination generated the desired tetrafluoro cyclohexane **1.122** as well as a trifluorocyclohexene (**1.121**) in equal ratios.[95] Through further studies, including the deuterium labelling experiment, it was established that **1.121** derived from the difluoro isomer **1.117**, which undergoes an elimination reaction and then phenonium ion rearrangement (intermediate **1.123**), followed by formation of the C-F bond with a retention of configuration (Scheme 1.35). [95,96]

Despite the undesired co-product (**1.121**), the synthesis is suitable for generating gramme quantities of all-*cis*-1,2,4,5-tetrafluoro-3-phenylcyclohexane for further applications.



Scheme 1.35: Synthesis of all-*cis*-1,2,4,5-tetrafluoro-3-phenylcyclohexane and fluorination of ditriflate [$^2H_2$]-99; i) Li, NH_3, quantitative; ii) *m*CPBA, DCM, 85%; iii)$Et_3N.3HF$, 140 °C; iv) Tf_2O, pyridine, CH_2Cl_2 , -10 °C to rt, 90% over two steps; v) $Et_3N.3HF$, THF, 100 °C, 100 (31%), 101 (42%).[95]

In this context, several studies have been conducted, involving electrophilic aromatic substitution reactions to prepare the nitro, bromo and iodo derivatives of tetrafluorophenylcyclohexane. These products then used to generate a range of tetrafluoro motifs, including aryl pyrroles, benzaldehydes, benzoic carboxylic acids and phenylalanine derivatives (Figure 1.12). [95,97,98]

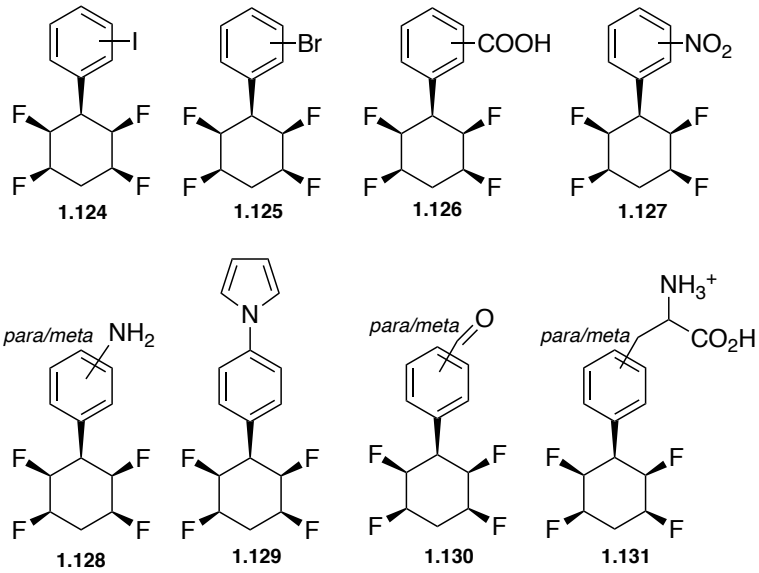


Figure 1.12: Tetrafluoro motifs synthesised in St Andrews. [95,97,98]

These products all have an aryl group attached to the cyclohexane. The next objective was to create building blocks, which have functional groups attached directly to cyclohexane ring and then develop these into more complex products such as potential drug precursors and peptidomimetics. Tetrafluorophenylcyclohexane **1.122** became a key starting material for this programme.

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Chapter 2. Synthesis of tetrafluorinated cyclohexane amino acid and pentafluorinated cyclohexane motifs.

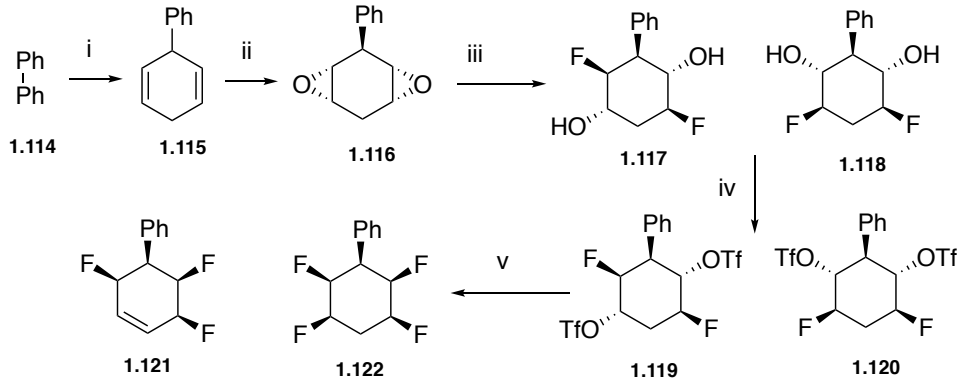
2.1. Introduction and objectives.

The novel properties associated with all-*cis*-fluorinated cyclohexanes have stimulated the development of synthetic methods to expand the structural diversity of these unusual building blocks. As described in Chapter 1, the all-*cis*-2, 3, 5-6 tetrafluorophenylcyclohexane motif **1.122**, is a valuable building block with potential in different research programs. [1,2] The phenyl ring of this motif was found to be amenable to a range of electrophilic aromatic substitution reactions, which has provided range of valuable intermediates, including the eventual incorporation of this motif into amino acids.[3–5] To date, such transformations have been performed exclusively on the phenyl ring, while the rest of the motif has remained untouched.

The prospect of introducing functional groups starting from radical bromination at the benzylic position of this moiety became the next objective. To this end, transformations of benzylic bromide **2.1** were investigated in a variety of directions in order to generate a range of new building blocks.

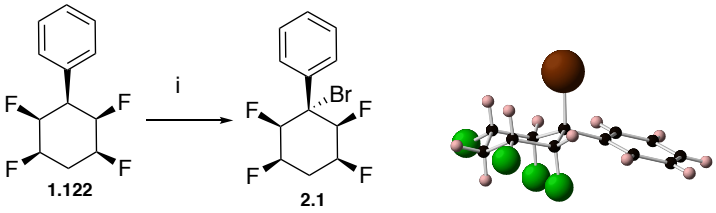
2.2. Route towards fluorinated amino acid.

All-*cis*-2, 3, 5, 6-tetrafluoro-cyclohexane **1.122** was prepared through the 5-step procedure as previously described in Chapter 1 and was the starting point for the preparation of all compounds in this study (Scheme 2.1). [1, 2, 5]



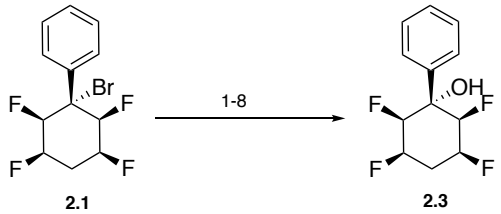
Scheme 2.1: Synthesis of all-*cis*-1,2,4,5-tetrafluoro-3-phenylcyclohexane; (i) Li, NH_3, quantitative; (ii) *m*CPBA, DCM, 83%; (iii) Et_3N. 3HF, 140 °C; (iv) Tf_2O, pyridine, CH_2Cl_2 , -10 °C to rt, 75% over two steps; (v) Et_3N.3HF, THF, 100 °C, 1.121 (28%), 1.122 (30%).[5]

With **1.122** in hand, benzylic bromination was explored through radical bromination using NBS in carbon tetrachloride (Scheme 2.2). This reaction proved very successful giving **2.1** as a single isomer in good yield. The structure and stereochemistry of **2.1** were confirmed by X-ray analysis (Scheme 2.2).



Scheme 2.2: Radical bromination of 2, 3, 5, 6 -all-cis-tetrafluroro phenyl cyclohexane; NBS, CCl_4/ MeCN (10/1), *hv*, reflux, 42 h (89%).

The next objective was to replace the Br by nitrogen in order to obtain an amine. Treatment with sodium azide in DMF was carried out (Table 2.1). Unfortunately, each attempt with altering the reaction conditions led solely to substitution of the bromine at the benzylic position by an hydroxyl group, resulting in tertiary alcohol **2.3**.[6] Further studies to investigate the mechanism of this unexpected reaction revealed that the reaction proceeds exclusively in DMF solvent and does not require the presence of NaN_3 and does not proceed in the presence of water (Table 2.1).

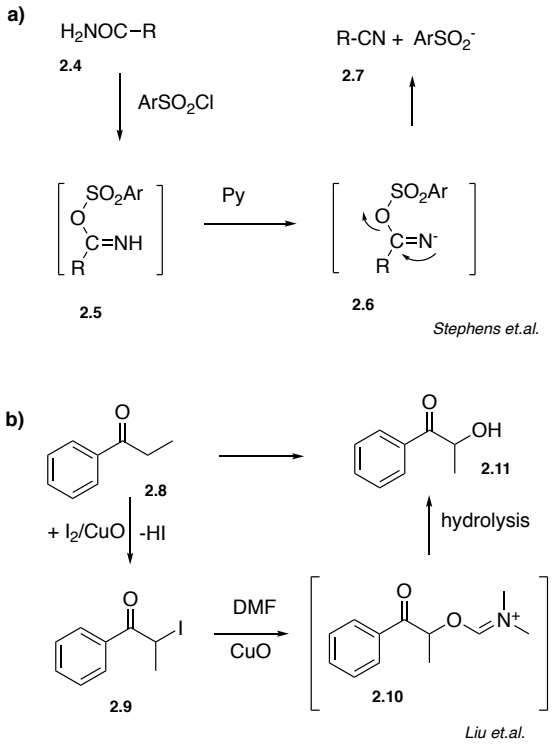


Entry	Solvent	NaN_3	H_2O[a]	Conversion[b]
1	DMF	present	absent[c]	100%
2	DMF	absent	absent	100%
3	DMF	absent	5%	0%
4	MeOH[d]	present	absent	0%
5	MeOH[d]	present	5%	0%
6	DCM[d]	absent	absent	0%
7	DCM[d]	absent	5%	0%

Table 2.1: Scope of reactions varying different conditions. All reactions have been done at 90 °C; [a] 5% of H_2O was added to reaction; [b]Conversion from 2.1 to 2.2 has been determined by ^{19}F NMR; [c] Reaction has been done in flame dried molecular sieves; [d] Reaction has been conducted in pressure tube at 90 °C.

The participation of the DMF in substitution reactions, has been observed in a number of studies, such as that of Stephens *et al.* who described the reactivity of primary amides (**2.4**)

towards sulfonyl chlorides resulting in an efficient conversion to corresponding nitriles (**2.7**) (Scheme 2.3, a).[7,8]

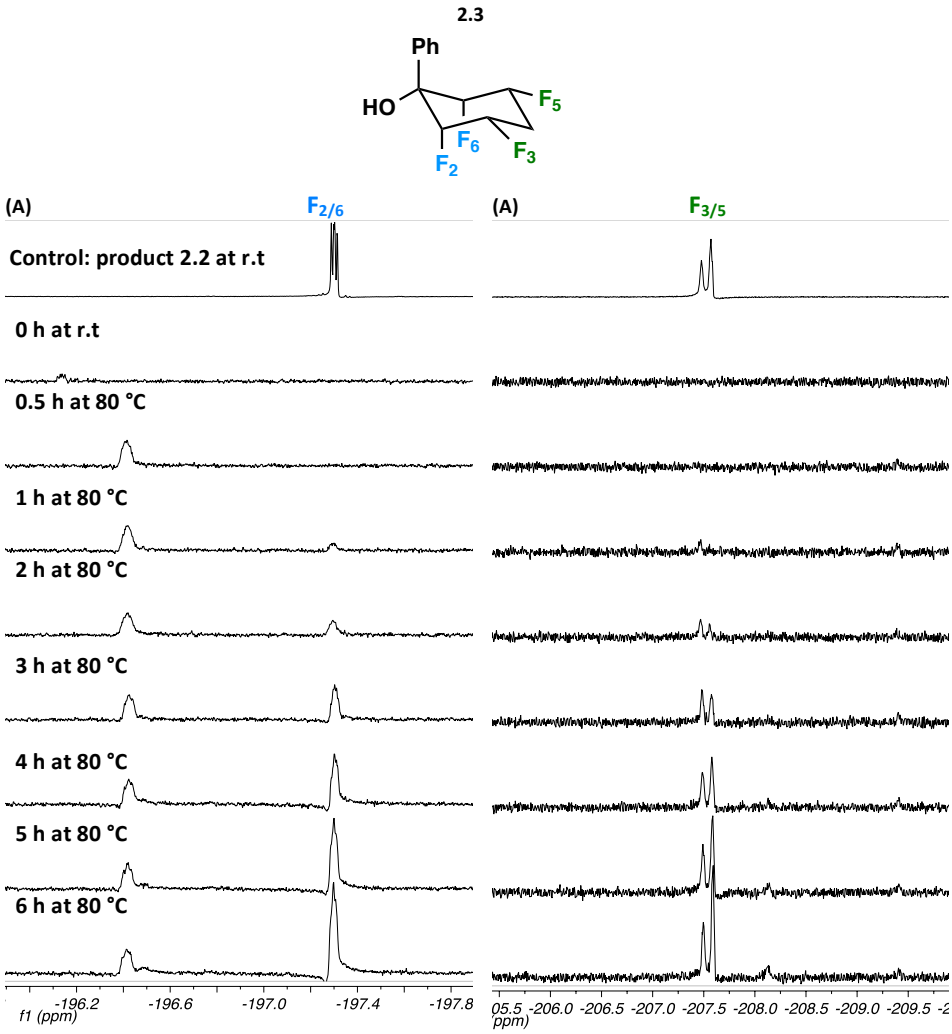


Scheme 2.3: a) The proposed O-sulfonation step of primary amide in order to form corresponding nitrile; b) Proposed mechanism for α –hydroxylation.[7,9]

The most recent and relevant work concerning DMF reactivity was reported by Liu *et al.* who described α-hydroxylation of α-iodoketone **2.9** using DMF as an oxygen source. Following an initial iodination of propiophenone **2.8** to generate **2.11**, nucleophilic attack by DMF resulted in the formation of putative intermediate (**2.10)** which then decomposed to give α-hydroxyl ketone (**2.11**) (Scheme 2.3, b).[9]

VT ^{19}F NMR studies

In order to explore if the reaction progresses through an intermediate such as **2.10** involving DMF as described by Liu *et.al* and shown on Scheme 2.3, the reaction with **2.1** was conducted in an NMR tube and carried out directly in an NMR machine, at 80 °C using DMF as a solvent. The formation of the new signals (δ -196.4 ppm and 208.2 ppm) (Figure 2.1, section A and B) close to the chemical shifts of the product were observed. The new signal at δ -196.4 ppm appeared after just 1 h at 80 °C and at 2 h a second signal at δ -197.4 ppm start to appear and then increased with time (Figure 2.1, A). A similar effect was also observed for the signal at δ -207.4 ppm after 1 h and then it starts to split into two peaks after 2 h, with a gradual increase over the time of the second signal (at δ -207.6 ppm) (Figure 2.1, B).



It is noteworthy that when purified product alcohol **2.3** is dissolved in DMF and heated at 80 °C, a similar NMR pattern to that found with **2.1** in DMF (δ 207.4 and 207.6 ppm) is observed (Figure 2.1, B). This suggests the reversible formation of an intermediate such as **2.2**.

Figure 2.2 compares the ^{19}F $\{^{1}H\}$ NMR of reaction (A) to the starting material **2.1** (B) and to the previously prepared product **2.3** (C) at room temperature In DMF. The product formed during the reaction is sufficiently similar to the control in order to assume that they are the same tertiary alcohol **2.3**.

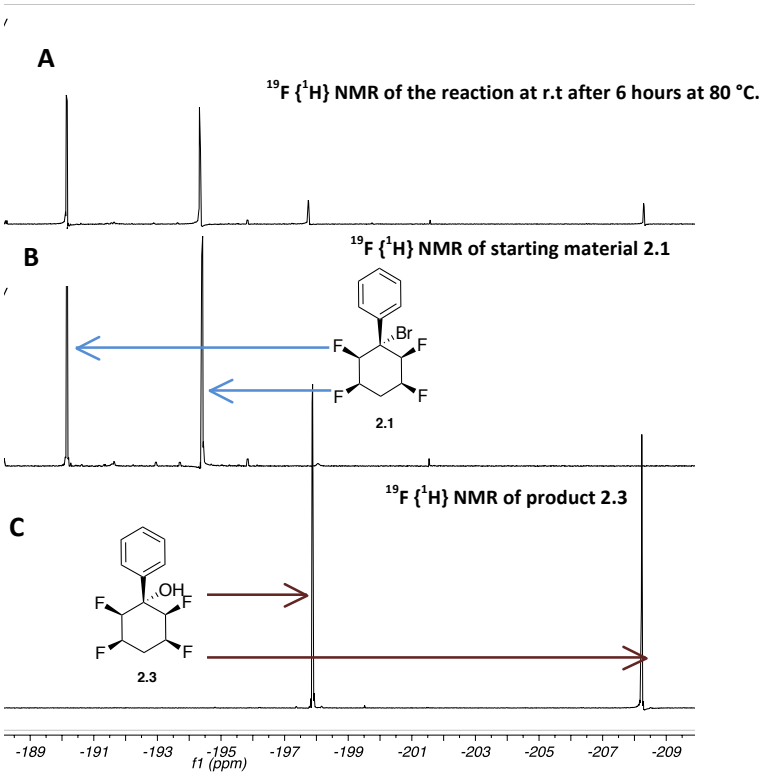
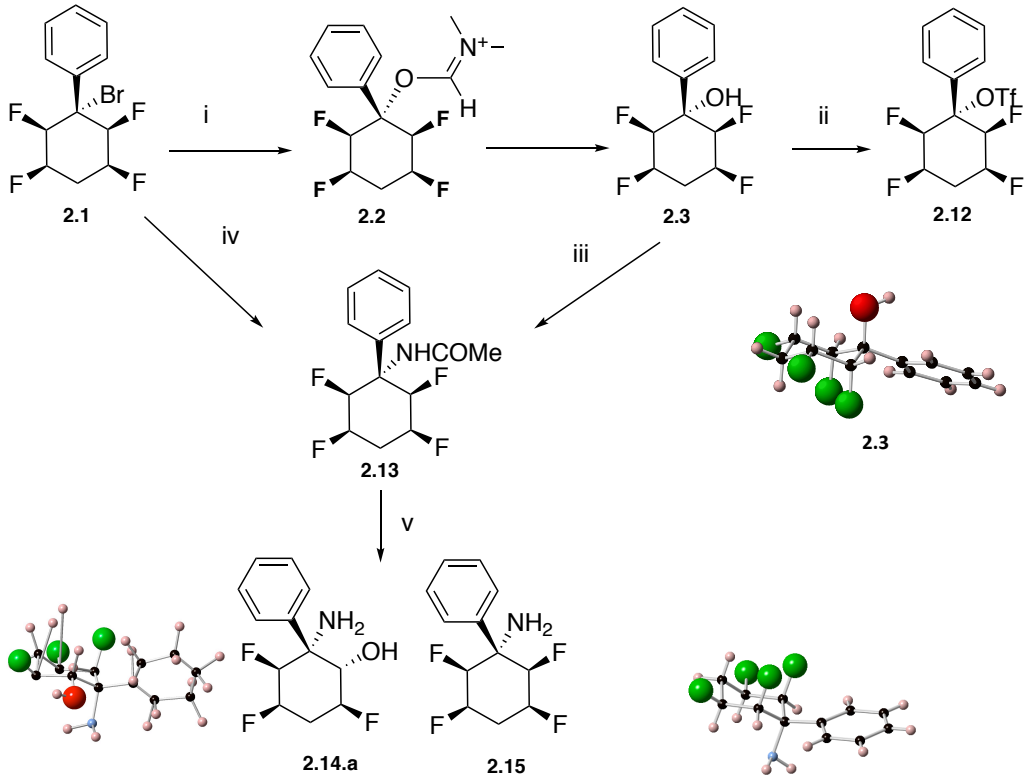


Figure 2.2: ^{19}F {^{1}H} NMR: (A) the reaction at r.t after 6 h at 80 °C; (B) starting material 2.1 ; (C) Reference sample of product 2.2; Samples were in DMF and recorded with D_2O probe.

An X-ray structure of product alcohol **2.3** (Scheme 2.4) demonstrated that the stereochemistry had the hydroxyl group on the opposite face of the cyclohexane ring to the fluorine atoms. This suggests direct nucleophilic attack to the hydrogen face of the ring through an S_N1 pathway, with the nucleophile attacking opposite to the fluorine atoms.

As an alternative approach to access an amine derivative it was decided to investigate a Ritter reaction with **2.3**, which involves acetonitrile as a solvent as well as a nucleophile. [8,19] Accordingly when a solution of **2.3** in acetonitrile was heated under reflux with the addition of sulfuric acid (2%), an efficient reaction took place to generate acetamide **2.13** (68% yield), the anticipated Ritter product. Compound **2.3** was also used to obtain triflate derivative **2.12** through the use of triflic anhydride in pyridine (Scheme 2.4, ii). Acetamide **2.13** was also obtained directly from benzyl bromide **2.1**, following the same procedure as show on Scheme 2.4 (reaction iii).

HCl-promoted hydrolysis of the acetamide **2.13** lead to two products in an approximate ratio of 3:2 (^{19}F NMR, Section 8.1.1). The major product was the anticipated free amine **2.15** however the minor product proved to be amino alcohol **2.14.a** (Scheme 2.4).



Scheme 2.4: (i) DMF, 90 °C, 16 h (82%); (ii) Tf_2O, Py, 0°C, 20 min, rt, 16 h (54% [illegible] h, (68%); (iv) MeCN, H_2SO_4, reflux, 48 h, (72%); (v) 6M HCl, 6 h, reflux, 2.14.a (15%), 2.15 (35%);

It was important to determine the configuration of the OH group, which had replaced one of the fluorine atoms. This was achieved by NMR analysis including 2D ^{19}F, ^{1}H HOESY NMR experiments.

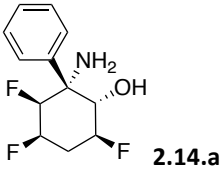
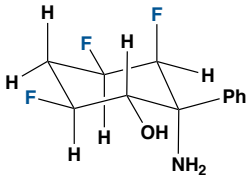
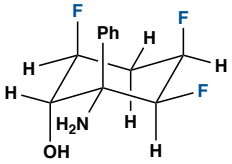
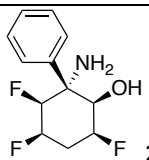
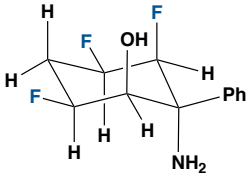
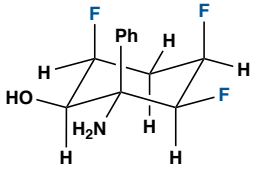
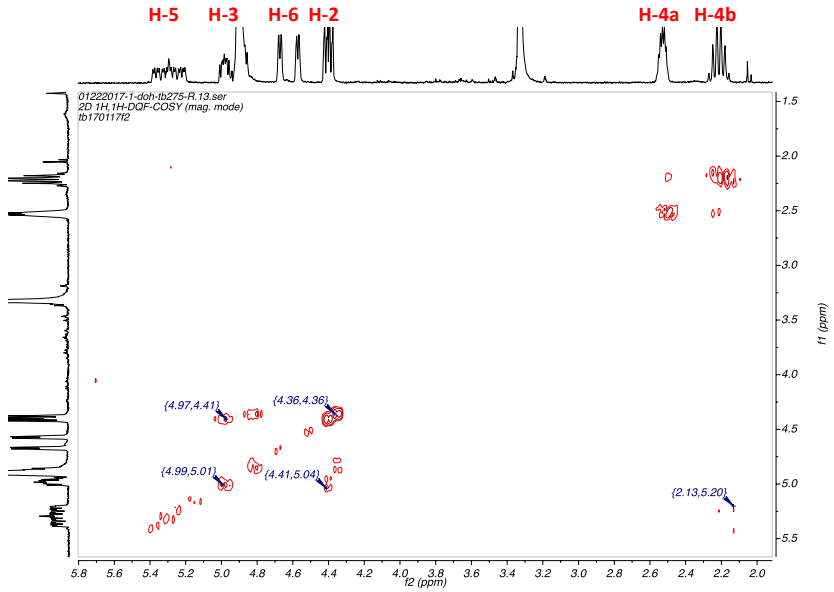
Configuration	Chair Conformation	
 **2.14.a**	 **(eq.)**	 **(ax.)**
 **2.14.b**	 **(eq.)**	 **(ax.)**

Table 2.2: Two stereochemical configurations (a and b) of compound 2.14 and four different chair conformations of compound 2.14 (eq. and ax.).

The assignment of the ^{1}H NMR spectrum of **2.14.a.** was secured by 2D homonuclear correlation spectroscopy (COSY) (Figure 2.3, A) and 2D Heteronuclear correlation spectroscopy (HOESY) (Figure 2.3, B).

(A) *2D ^{1}H, ^{1}H-DQF-COSY NMR (300 MHz, MeOD)*



(B) *2D ^{1}H, ^{19}F HMBC NMR (377 MHz, MeOD)*

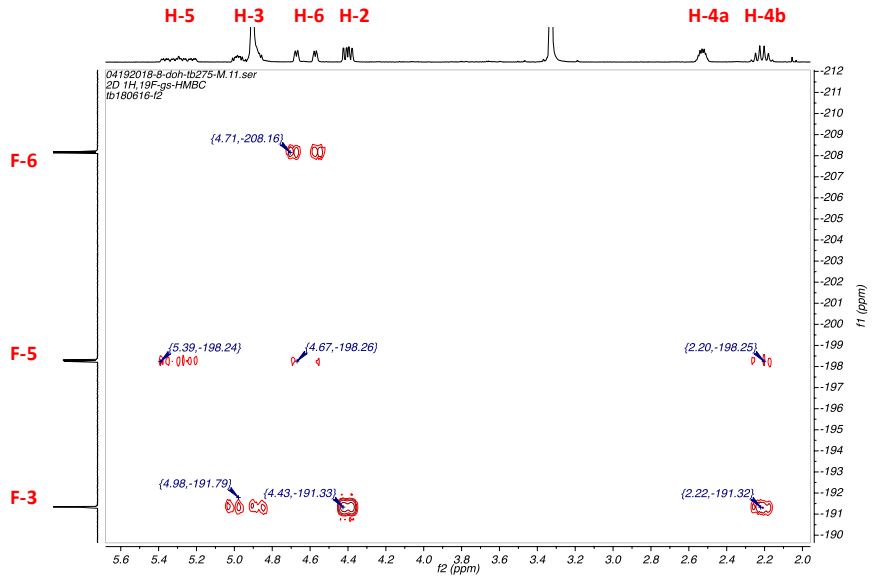


Figure 2.3 (A) 2D ^{1}H, ^{1}H-DQF-COSY NMR spectrum of 2.14.a at rt in MeOD; (B) 2D ^{1}H, ^{19}F HMBC NMR spectrum of 2.14.a at rt in MeOD.

Considering the two possible configurations (**2.14.a** and **2.14.b**) shown in Table 2.2, each can have two chair conformations, with the phenyl group in an equatorial (**eq.**) or an axial (**ax.**) orientation.

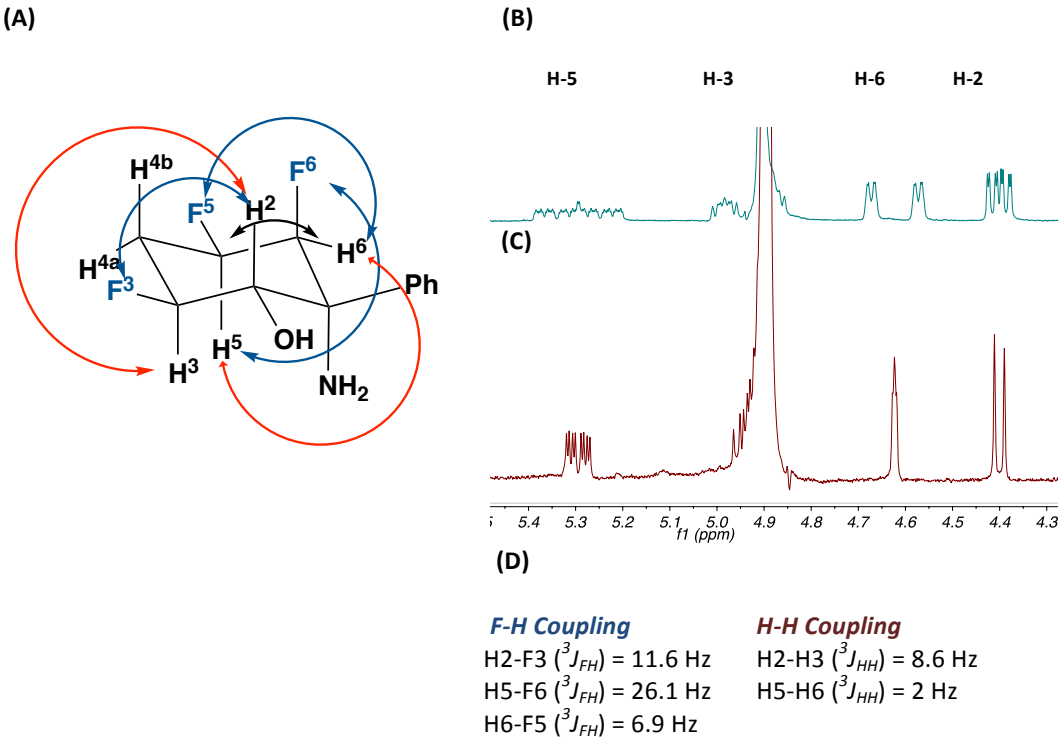


Figure 2.4: (A) Proposed conformation and configuration of compound 2.14.a; (B) ^{1}H NMR NMR (400 MHz, MeOD) of 2.14.a; (C) ^{1}H with {^{19}F} decoupling NMR (400 MHz, MeOD); (D) $^{3}J_{FH}$ and $^{3}J_{HH}$ coupling constants of interest.

H-H coupling constants

A straightforward Karplus analysis is helpful. A large H,H vicinal coupling constant of $^{3}J_{HH}$ = 8.6 Hz is observed for H2-H3, which is consistent with an antiperiplanar arrangement relative to each other, as shown on structure **2.14.a** (**eq.**) (Figure 2.4).[34,35] If the OH configuration was inverted, then a lower coupling constant would be anticipated for $^{3}J_{HH}$ for H2-H3. This coupling constant can be compared to that of $^{3}J_{HH}$ of H5-H6, which is only 2 Hz. H5 and H6 are '*gauche*' in relation to each other, consistent with this low value (Figure 2.4).[34,35]

F-H coupling constants

A comparison of the H2-F3 and H6-F5 $^{3}J_{HF}$ coupling constants are also helpful. It can be seen from Figure 2.4 (D) that the $^{3}J_{FH}$ for H2-F3 coupling constant is 11.6 Hz and that for H6-F5 $^{3}J_{FH}$ =6.9 Hz. The difference in these values is significant and is consistent with the H2 axial and

F3 equatorial arrangement having a larger coupling constant than H5 and F6, where both F and H are equatorial and will lower value.[36] In addition to these observations, a larger $^{3}J_{FH}$ coupling constant of 26.1 Hz for H5-F6 was observed, which is consistent with both H5 and F6 in an antiperiplanar allignment.[36]

Through space correlation

In order to further explore the preferred solution state conformations of **2.14.a**, 2D ^{19}F Heteronuclear NOESY (HOESY) experiments were conducted by sequentially irradiating the fluorine signals corresponding to F-3, F-5 an F-6 (Figure 2.5 for F-6, Experimental section 7.3.1, Figure 1 for F-3 and F-5). This allows identification of hydrogen atoms that are close in space to the fluorines. Upon irradiation of F-6, the 2D HOESY NMR experiment showed a through space correlation to the H-2 proton (Figure 2.5, B). This suggesting a diaxial relationship between H2 and F-6 consistent with conformer **2.14.a. (eq.).** No correlation was observed between any other proton or fluorine environments (Experimental section 7.3.1, Figure 1, C, D), suggesting that the other possible conformers shown in Table 2.2 are not relevant.

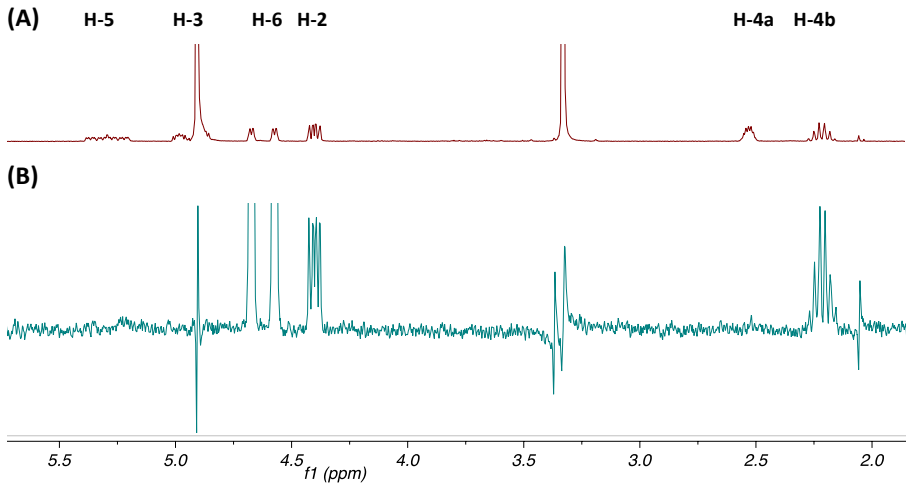


Figure 2.5: A) ^{1}H NMR Spectrum of 2.6 in MeOD; B) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-6 at rt.

The $^{3}J_{HH}$, $^{3}J_{FH}$ coupling constants and the HOESY NMR data support a structure for **2.14.a**, where the amine and alcohol groups are *syn* to each other and that fluorine was replaced by OH, with a retention of configuration.

A mechanism for the formation of **2.14.a** is proposed which is consistent with an intermolecular displacement of fluoride by the acetamide carbonyl, followed by

participation of the phenyl ring through a phenonium intermediate **2.20** and then attack by water as shown in Scheme 2.5. [10–15] Several experiments were carried out altering the conditions of HCl hydrolysis in an effort to find optimum conditions favouring **2.15**, however neither altering the temperature or changing HCl concentrations affected the outcome of the reaction (Table 2.3).

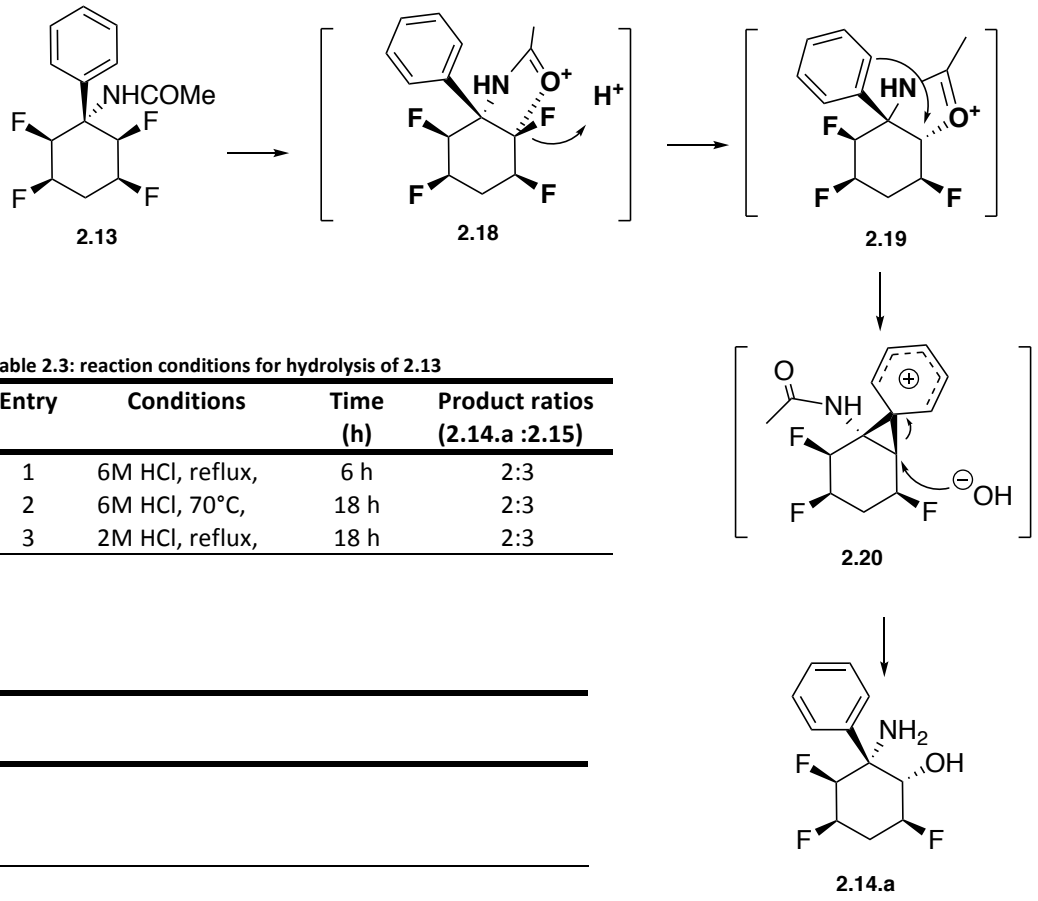
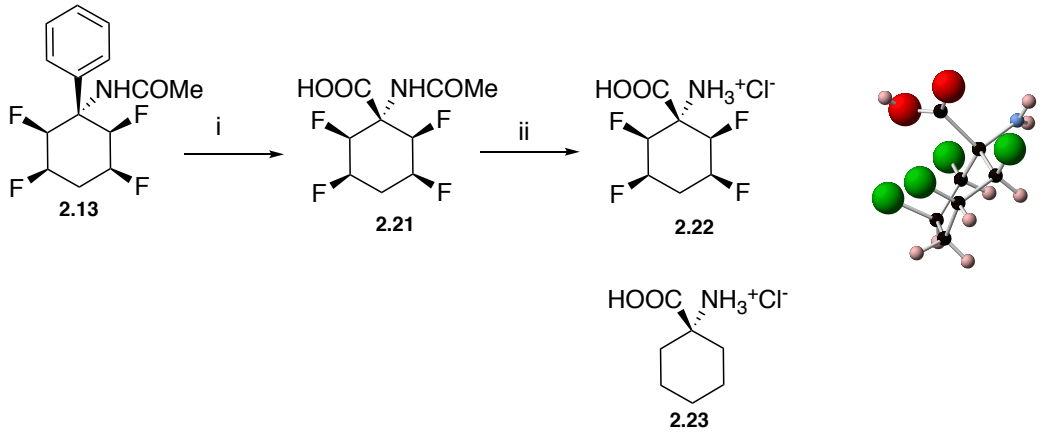


Table 2.3: reaction conditions for hydrolysis of 2.13

Entry	Conditions	Time (h)	Product ratios (2.14.a :2.15)
1	6M HCl, reflux,	6 h	2:3
2	6M HCl, 70°C,	18 h	2:3
3	2M HCl, reflux,	18 h	2:3

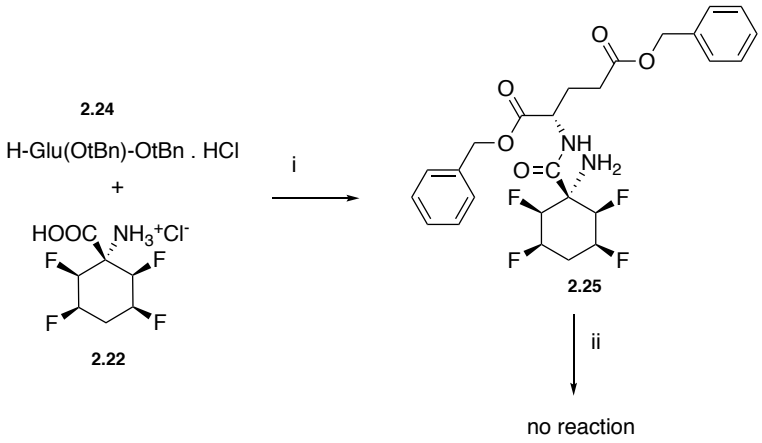
Scheme 2.5: Proposed mechanism for formation of byproduct 2.14.a

It became an objective to cleave the phenyl ring and convert it to a carboxylic acid derivative. The carboxylic acid amide derivative **2.21** was obtained by oxidative degradation of the phenyl ring of **2.5** using a catalytic amount of ruthenium trichloride hydrate and periodic acid under the biphasic (CCl_4/H_2O/MeCN) solvent system described by Sharpless *et.al.* (Scheme 2.6).[16] Hydrolytic cleavage of acetamide **2.21** proceeded in a smooth manner furnishing the all-*cis*-2, 3, 5, 6- tetrafluorocyclohexane amino acid **2.22** (Scheme 2.6), this time without any accompanying hydroxydefluorination side product as was previously observed in the conversion of **2.13** to **2.15**.[17]



Scheme 2.6: Preparation of amino acid 2.22: (i) H_5IO_6, 5% $RuCl_3$, CCl_4, reflux, 42 h (61%); (ii) 6M HCl, 16 h, reflux (55%);

The amino acid **2.22**, which was prepared with an overall yield of 4% in nine steps, is an analogue of the well described cyclohexyamino acid **2.23** (Scheme 2.6). This latter amino acid has found relatively wide application as a non-proteinogenic amino acid.[18–20] This entirely novel fluorinated amino acid opens up the possibility of introducing the tetrafluoro cyclohexane motif into peptides in a similar manner.



Entry	Reaction conditions	Result
1	Fmoc-Gly-OH, EDCI, HOBt, NMM, DMF. [a, b, c, d, e]	N/a
2	Fmoc-Gly-OH, TBTU, HOBt, DIPEA, DMF, [a, b, c]	N/a
3	Fmoc-Gly-OH, PyBOP, DIPEA, DMF, [a, b, c]	N/a
4	DIC, HOBt, DMF, [a, b, c, d, e]	N/a
5	Fmoc-Gly-Cl, DCM, reflux, [a. d,]	N/a
6	Fmoc-Gly-F*, DIPEA, DCM, reflux, [a, d] .	N/a

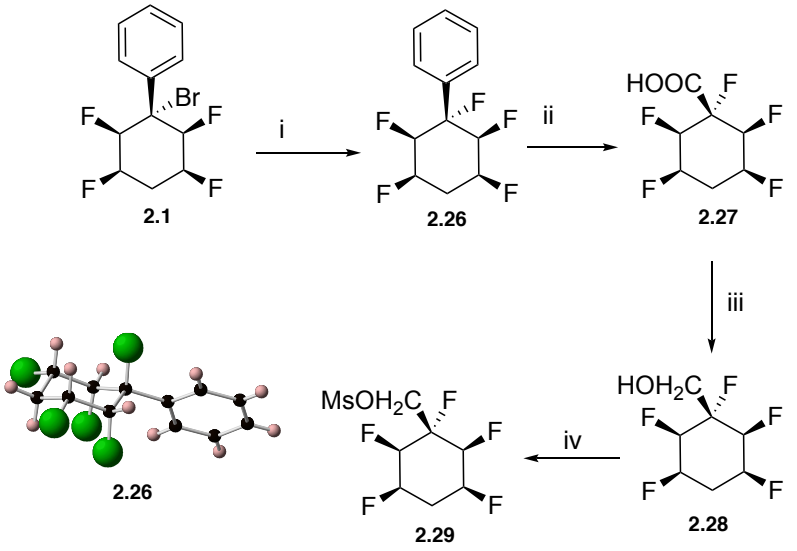
Scheme 2.7: (i) EDCI, HOBt, NMM, DMF, rt, 18 h (38%); Reaction conditions for reaction (ii); [a] rt, 18 h; [b] 60 °C, 18 h; [c] 100 °C, 18 h; [d] Pressure tube, 100 °C, 18 h; [e] Pressure tube, 200 °C, 18 h; 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI); (1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU); 1-hydroxy-1H-benzotriazole (HOBt); N,N-Diisopropylethylamine (DIPEA); Fmoc-Gly-F* was synthesised according to the literature procedure described in Supplementary, section 7.2.[22]

In order to explore the reactivity and properties of all-*cis*-fluorinated amino acid **2.22**, a tripeptide, Gly-Pro-Glu (GPE) analogue, was synthesised.[21] The GPE tripeptide analogue was chosen for its known neuroprotective activity and its structural simplicity.[21] As such, it was utilised as a promising starting point for the development of peptodidomimetics with this new motif.

Coupling the C-terminus of **2.22** to glutamic acid dibenzyl ester (**2.24**) lead to the formation of dipeptide **2.25** (Scheme 2.7). However, the subsequent coupling of the N-terminus to Fmoc-Glycine, was unsuccessful. Several reaction conditions were tried, including various coupling reagents and harsher reaction conditions (Scheme 2.7), though none afforded any reaction at the amine. As such, the N-terminus proved to be unreactive. This is most likely due to the fact that in addition to being a quaternary amine it is also in close proximity to electron withdrawing fluorine atoms rendering it a poor nucleophile.

2.3. 1,2,3,5,6-Pentafluoro cyclohexane motifs.

A particularly efficient reaction in this study involved a transhalogenation reaction of benzyl bromide **2.1** to benzylfluoride **2.26** using silver (II) fluoride in diethyl ether (Scheme 2.8). The stereochemistry of **2.26** was solved by X-ray crystallography (Scheme 2.8) and in the same manner as products **2.1** and **2.3**, the structure indicates substitution with retention of configuration.



Scheme 2.8: (i) Ag(II)F, $(C_2H_5)_2O$, reflux, 20 h (82%); (ii) H_5IO_6, 5% $RuCl_3$, reflux, 42 h (74%); (iii) BH_3.THF, THF, 16 h, 50 °C (55%); (iv) MsCl, Et_3N, DCM, 0 °C, 0.5 h, then RT, 18 h (63 %).

The phenyl ring in pentafluoro cyclohexane **2.26** was then subjected to oxidative cleavage using a ruthenium tetroxide complex to successfully furnish carboxylic acid **2.27** (Scheme 2.8). It is notable that direct oxidation of phenyl all *cis*-2, 3, 5, 6 –tetrafluoro-cyclohexane **1.122** by this method is ineffective, as the presence of the α-hydrogen, leads to HF elimination and breakdown.[22] However with **2.26**, the fluorine atom operates as a block group to prevent HF elimination, forming carboxylic acid **2.27**, which is stable and relatively easy to isolate.

Reduction of carboxylic acid **2.27** with borane tetrahydrofuran furnished pentafluoro cyclohexane alcohol **2.28**.[16] This pentafluoro alcohol **2.28** was found to sublime under reduced pressure and was volatile at atmospheric pressure. In an effort to temper this volatility, **2.28** was converted to mesylate **2.29** using mesyl chloride in order to make an intermediate that was ready for further transformations to introduce the pentafluorocyclohexyl motif into higher molecular architectures if necessary.[23]

2.4. α-Fluoroamide conformations.

2.4.1. Previous research

Carboxylic acid **2.26** offers an attractive building block for bioactives research, and in this context it became of interest to explore α-fluoroamide derivatives that can be obtained from **2.26**. [24,25] α-Fluoroamide conformations have been the subject of significant interest in several peptide conformation studies. One such study by Banks *et al*., showed that α-fluoroamide derivatives such as **2.30** adopt a *trans*-planar conformation around the (O)C-C(F) bond in the solid state with a deep potential minimum of up to 8 kcal mol^{-1} (Figure 2.6).[24]

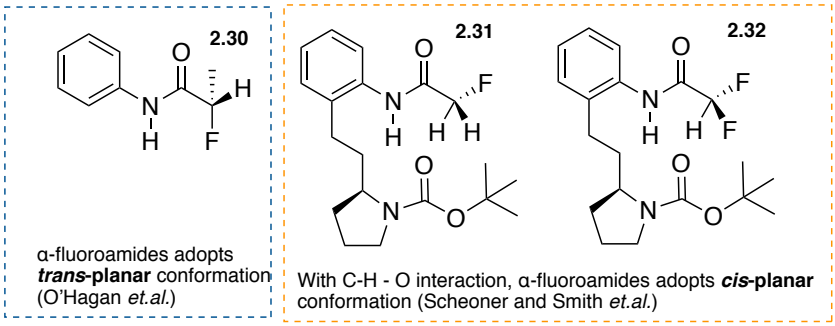


Figure 2.6: Outline of the previous work regarding α-fluoroamide conformations by Banks *et.al* and Jones *et.al.*[24,25]

The conformation is favored as there is decreased repulsion between the carboxyl oxygen and the fluorine and a strong CF…H(N) electrostatic attraction. This gives an overall dipolar relaxation between the amide and C-F dipoles.[26] Jones *et al.,* however, revealed that these preferential conformations can be intercepted by inter- and intra-molecular hydrogen bonds, such as in compound **2.31**, and this phenomenon is further enhanced upon the introduction of a second fluorine (compound **2.32**), making the C-H a stronger H-bond donor (Figure 2.6). [24]

2.4.2. DFT model calculations

In order to study the intrinsic rotational preferences of the fluorinated carboxyamides, a conformational analysis was performed by professor Michael Buehl for α-fluoro methylamide **2.33** (Figure 2.7) as a model amide at the $B3LYP^{i}$/6-311+G** level of density functional theory.[26–29] After initial optimisation to find the minima in each case, full rotational energy profiles were constructed through relaxed scans of the F-C-C=O dihedral

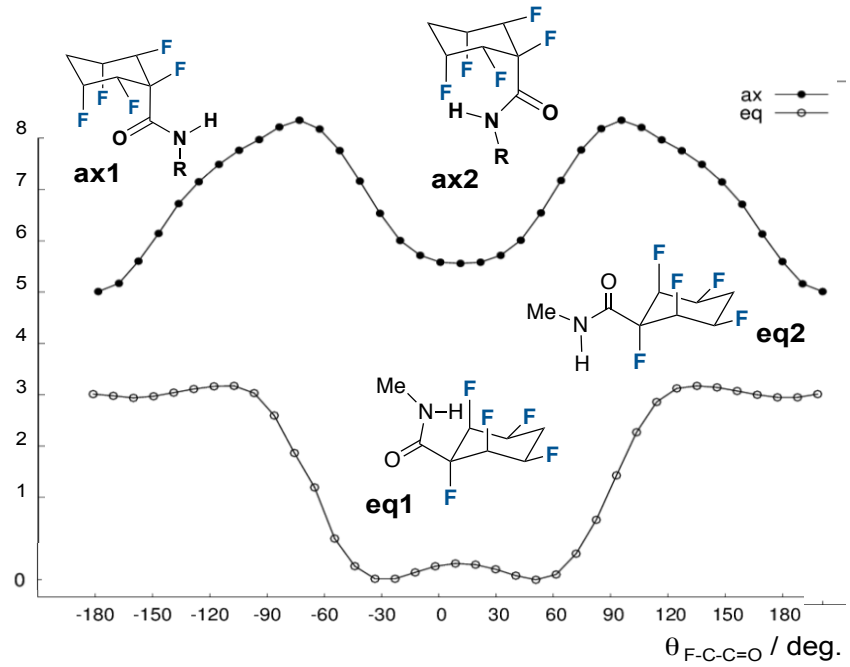


Figure 2.7: α-fluoromethylamide 2.31 as a model amide at the B3LYP[ii]/6-311+G level of density functional theory**

Figure 2.8: Rotational energy profiles about the C(F)-C(=O) bond in model methylamide 2.33 for the target conformations in gas phase (B3LYP/6-311+G level). Energies are in kcal mol^{-1} relative to the most stable conformer (eq1).**

angles (θ) frozen at values in steps of 10° and minimizing the rest of the molecule. The resulting profiles are displayed in Figure 2.8.

Within these profiles, higher-lying minima were apparent, and were subjected to full geometry optimisations, affording rotamers **ax2** and **eq2**. Relative energies and salient geometrical parameters of all minima are shown in Table 2.4. While **ax1** and **ax2** are essentially C_s-symmetric with dihedral angles θ of 180° and 0°, respectively, **eq1** and **eq2** are lacking such planes of symmetry and come in enantiomeric pairs (though separated by very low energy barriers, cf. lower profile in Figure 2.8).

As expected, there is a preference for the bulkier amide group in the free model to be placed equatorial, rather than axial. This preference is rather pronounced in the gas phase, as the computed energy difference between **eq1** and **ax1** is 5.5 kcal mol^{-1}. However, there are significant variations of the dipole moments between the minima (see μ values in Table 2.4).

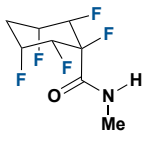
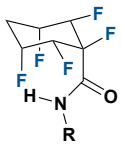
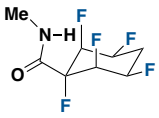
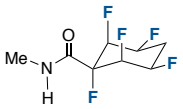
Property	Conformer of α-fluoroamide **2.33** ax1	ax2	eq1	eq2
				
ΔE_{rel} [kcal mol^{-1}] gas phase (ΔE_{rel} [kcal mol^{-1}] in water) [a]	5.6 (0.3)	6.1 (0.9)	0.0 (0.0)	3.5 (0.6)
$\theta_{F\text{-}C\text{-}C=O}$ calc [°]	179.9	-1.7	37.6	163.7
X-ray	*161.1* [b]	*n.a.*	*5.8* [c]	*n.a.*
nearest $d_{F\cdots H(N)}$ [Å] [d]	2.084	2.141	1.991	2.112
μ [D]	4.9	7.2	2.1	6.4

Table 2.4: Computed properties of α-fluoroamide 2.33 (energies Δ E_{rel} relative to eq1, dipole moments *m*, selected angles and distances) at the B3LYP/6-311+G level (gas phase values, unless otherwise noted).**

Thus, one may expect the equilibrium to be quite sensitive to the polarity of the environment. This sensitivity, the relaxed scan and subsequent optimisations were repeated using a polarizable continuum model (CPCM) representing water model (Figure 2.9). [30,31]

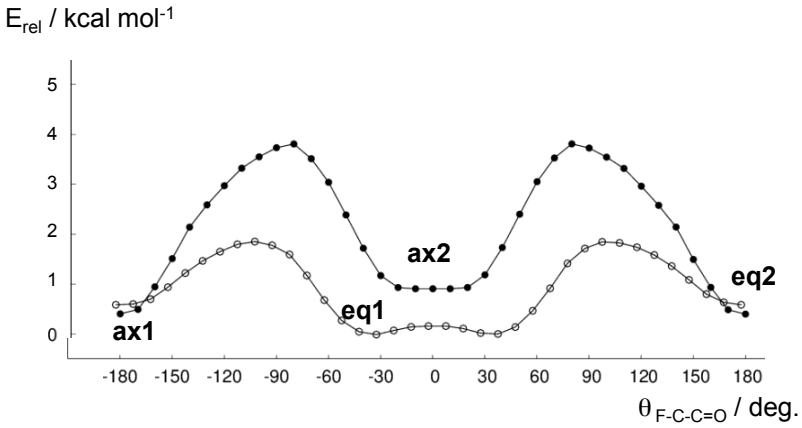
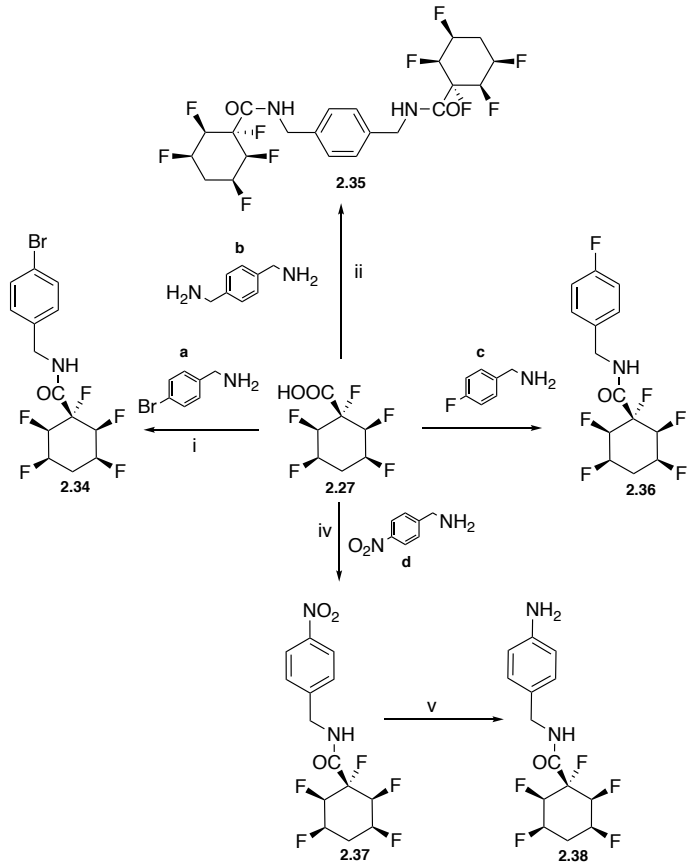


Figure 2.9: Rotational profiles about the C(F)-C(=O) bond in a simpler model of a fluoroamide 2.33 for the target compounds in a continuum modeling water(R = Me, CPCM/B3LYP/6-311+G level), energies given in kcal mol^{-1} relative to the most stable conformer (eq1).**

In this water solvent model the resulting profiles are shifted much closer toward each other (Figure 2.9), and the relative energies of all minima are within less than 1.04 kcal mol^{-1}. The conformer **eq1** emerges from this DFT study to be lowest in energy, whereas **eq2** conforms more to the classical α-fluoroamide conformation (Figure 2.9). However the data indicates that in a polar aqueous environment the comparative energies of all of the minima conformations are within 1 kcal mol^{-1} of each other hence, solution NMR analysis was conducted in order to investigate this conformational preference further.

2.4.3. Solid-state X-ray studies of benzylamides.

In order to analyse α-fluoroamide conformations by solid and solution phase studies, the carboxylic acid **2.27** was coupled with benzylamines **a**-**d**, which are distinguished by their *para*-aryl substitution (Scheme 2.9). Using standard coupling conditions with EDCI, HOBt and NMM, the four fluorinated carboxamides, **2.34**, **2.35**, **2.36** and **2.37** were obtained in good yields as illustrated on Scheme 2.9, indicating that carboxylic acid **2.27** is a good coupling partner despite being sterically demanding and carrying an electronegative fluorine adjacent to the carboxylic acid moiety.[32]



Scheme 2.9: (i) EDCI, HOBt, NMM, DMF, a, rt, 18 h (87%); (ii) EDCI, HOBt, NMM, DMF,b, rt, 18 h (70%); (iii) EDCI, HOBt, NMM, DMF, c, rt, 18 h (57%); (iv) EDCI, HOBt, NMM, DMF, rt, 18 h (82%); (v) $SnCl_2$. $2H_2O$, EtOH, 90 °C, 18 h (65%); Amine derivatives used: 4-Bromobenzylamine (amine a), 1,4-Phenylenedimethanamine (amine b), 4-fluorobenzylamine (amine c), 4-nitrobenzylamine (amine d)

In addition the *para*-nitrobenzyl amide **2.37** was then reduced to its corresponding amine **2.38** using stannous chloride. This treatment did not affect the amide or the tetrafluorocyclohexane ring system.[33]

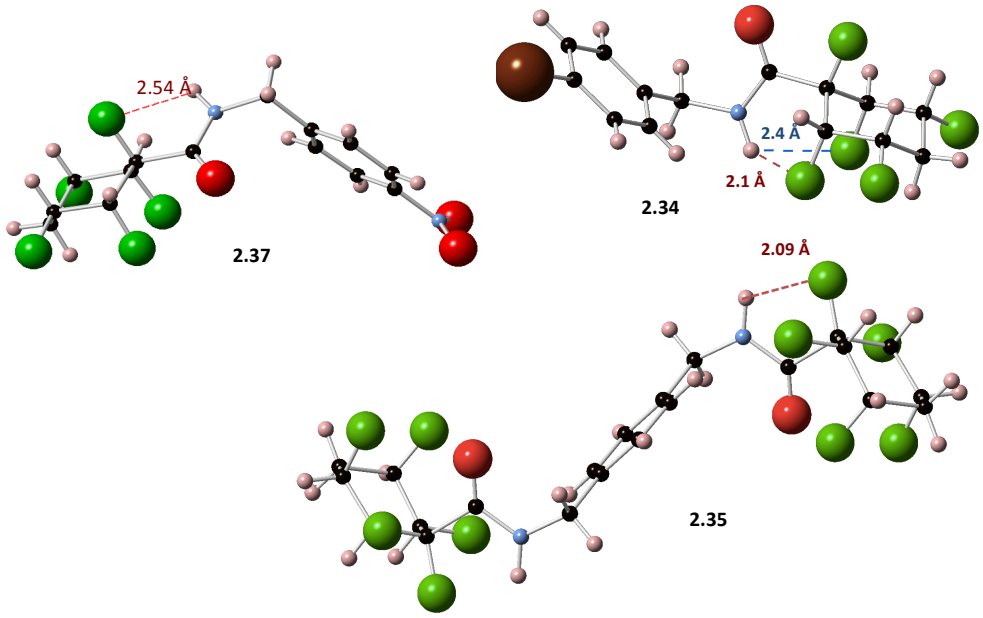


Figure 2.10: X-ray structures of carboxinimides 2.34, 2.35, 2.37

From the synthesised range of amide products, **2.34**, **2.35** and **2.37** generated suitable crystals for X-ray structure analysis(Figure 2.10).

Bis-amide **2.35** adopts **ax1** structure, which is a classical conformation of α-fluoroamide where amide oxygen is directed towards the two axial fluorines and distance between NH and α-fluorine being only 2.09 Å (Figure 2.10). This is an energy minimum by DFT and it is experimentally observed here.

The crystal structure of the brominated carboxamide (*p*Br) **2.34** (Figure 2.10) adopts the **eq1** conformation, which is the lowest energy calculated structure in the gas phase (Figure 2.8) and *iso*-energetic with the **ax1** structure in the solvent (H_2O) continuum model determined by DFT (Figure 2.9). In this conformation, the fluorine atom at C-1 lies '*cis*' to the carbonyl and N-H is positioned in between F-2 and F-6 with distances of 2.1 Å and 2.4 Å (see Figure 2.10). 2.1 Å is a very short distances for an intramolecular H---F contact suggests a stabilizing electrostatic interaction.[33]

Finally the X-ray crystal structure of amide **2.37** (*p*NO_2) shows that the N-H is orientated towards F-1 and is positioned at a distance of 2.54 Å, and simultaneously the oxygen on the carbonyl is twisted away from the F-2 and F-6 diaxial fluorines atoms at an angle of approximately 45°. This conformation most closely corresponds to the **eq1** conformation (F-C-C-O dihedral angle of 123 °C).

Accordingly to both, computational DFT analysis and X-ray structure analysis, **ax1** and **eq1** are two closely isoelectronic conformations for this class of α-fluoroamides.

2.4.4. ^{19}F HMBC and HOESY NMR studies.

In order to explore preferred solution state conformations relative to their solid state structures, ^{19}F HMBC and HOESY NMR experiments were conducted on compounds **2.34**, **2.35** and **2.37** in $CDCl_3$.

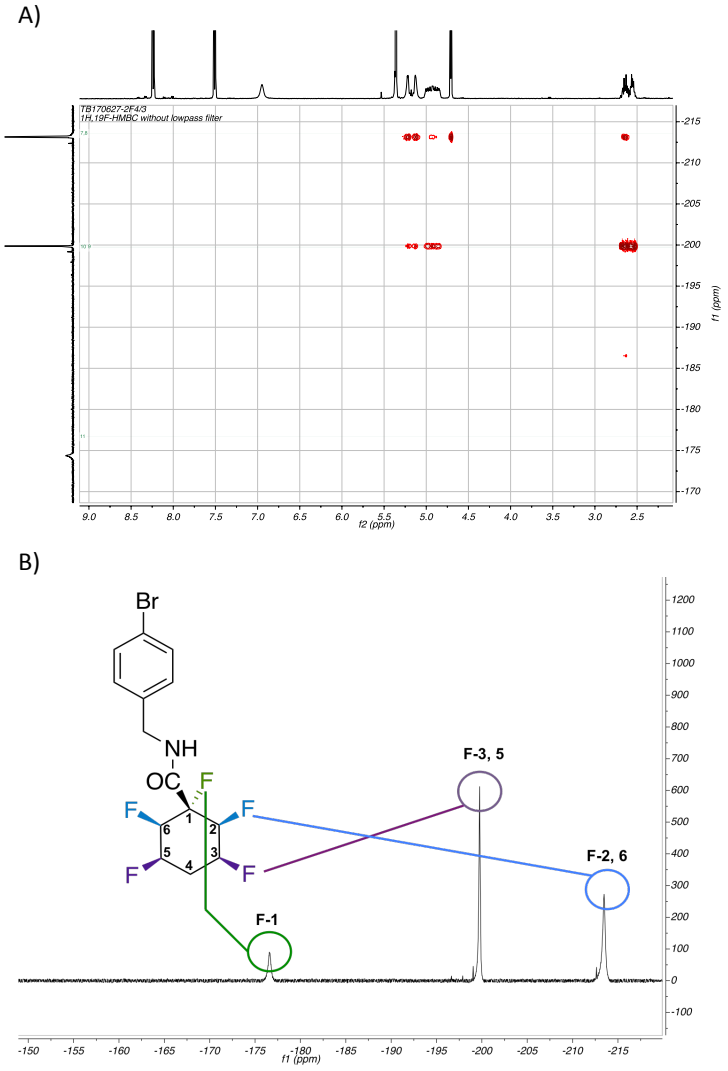


Figure 2.11: A) ^{19}F HMBC NMR spectrum of 2.34 in $CDCl_3$. B) ^{19}F with ^{1}H decoupling NMR spectrum of 2.34 along with the structure of 2.34, identifying the 3 fluorine peaks that relate to F-1, 2, 3, 5, 6 fluorine atoms.

^{19}F HMBC NMR analysis was initially performed on each carboxamide in order to assign each fluorine atom in the ^{19}F NMR spectrum (Figure 2.11). This was then followed by ^{19}F HOESY

NMR experiments, in order to define which hydrogen atoms have a close through space correlation to each of the fluorine environment (Figure 2.12).

Through space interactions to the proton of the amide N-H amide were expected to be especially diagnostic in differentiating the minimum energy conformations **ax1**/**ax2**/**eq1**/**eq2** that are defined in the DFT study.

As shown on Figure 2.12(E), ^{19}F-HOESY NMR spectra for **2.34** revealed a strong perturbation to the HN, H-2, 4[a] and 6 atoms during irradiation of F-2/6 fluorines, suggesting the dominance of conformer **eq1** in chloroform . No correlation at all to atoms H-3 and H-5 was detected, suggesting that conformer **ax2** is not relevant (Figure 2.12, E).

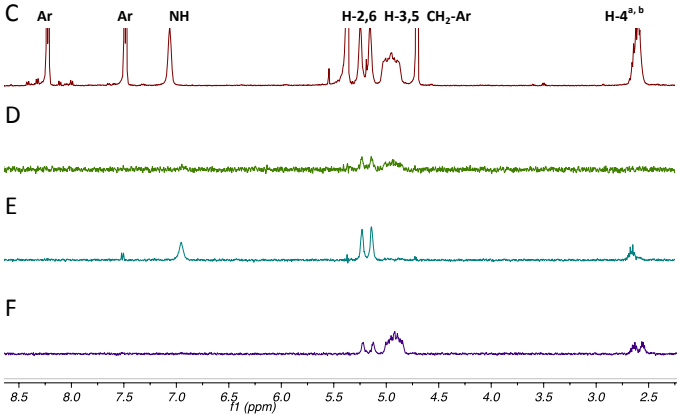


Figure 2.12: C) ^{1}H NMR Spectrum of 2.34 in $CDCl_3$. D) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-1 at rt. E) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-2 and F-6. F) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-3 and F-5.

The ^{19}F-HOESY NMR spectra for amides **2.35** and **2.37**, had a very similar outcome and are shown more fully in the Experimental section 7.3.2.

In addition to HOESY NMR studies, at the closer look on both ^{1}H {^{19}F} coupled and decoupled NMR spectrum of compound **2.34** (Figure 2.14, (B), (C)), the large coupling constant of $^{3}J_{HH}$ = 12.3 Hz is observed for H(3,5)-H(4a). In agreement with the Karplus equation, this coupling range supports **ax.1** conformation, where two H(3,5) and H-4a are antiperiplanar to each other, as shown on Figure 2.14 (A).[34,35]

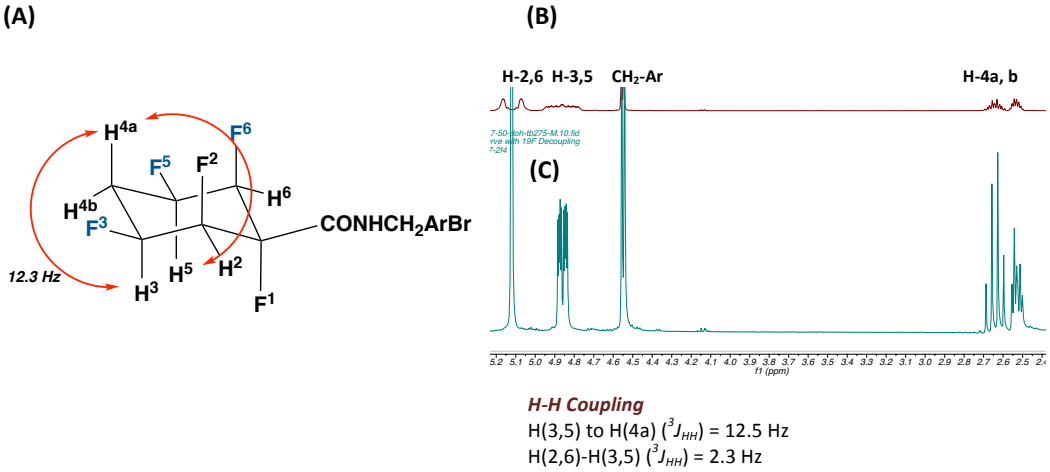


Figure 2.14: (A) Eq.1 conformation of compound 2.34; (B) ^{1}H NMR (400 MHz, $CDCl_3$) of 2.34; (C) ^{1}H with ^{19}F decoupling NMR (400 MHz, $CDCl_3$) of 2.34.

In solution the amides of carboxylic acid **2.27** do not seem to adopt the most favourable gas phase arrangement **eq2** (Figure 2.8), where the F-1 bond lies co-planar and *syn*-parallel to the amide N-H. This could be due to an alignment of the amide dipole with the two diaxial C-F bonds (F2/F6), which result in an increase of molecular diapole (Table 2.4). An alternative **eq.1** conformation emerges to be a preferred arrangement in chloroform, where sterically demanding carboxamide group lies equatorial, and the N-H hydrogen is able to pick up very short and presumably stabilizing F---H interactions with either of the two axial fluorines (F2/F6).

2.4. Conclusion

Radical bromination on all-*cis*-2, 3, 5, 6– phenyl tetrafluoro cyclohexane **1.122,** generated **2.1**, which became a substrate for further elaboration. Derivatives such as all-*cis*-tetrafluoro amino acid **2.22** and pentafluoro carboxylic acid **2.27** were prepared. Each of these has the potential to serve as a building blocks in chemical libraries. The stereochemical outcome (retention of configuration) of these reactions demonstrates the importance of the stereoelectronic properties of the fluorine during nucleophilic substitution. The polarity of the fluorine face creates an electron rich shield, which directs nucleophilic attack to the protic face of the cyclohexane ring.

Carboxylic acid **2.27** was readily coupled with benzylamines to prepare a range of α-fluoroamides. X-ray analysis of pentafluoro cyclohexane carboxamides **2.34**, **2.35** and **2.37**,

presented some insight into α-fluoroamide conformations, which were further investigated through ^{19}F HOESY NMR studies and DFT calculations. By comparing computational, solution and solid-state conformational results it was concluded that the rotational profile of the α-fluorocarboxyamides is influenced by several factors, including F--O repulsion, electrostatic attraction between NH—F, the amide's preference for adopting an equatorial orientation on the cyclohexane ring and intermolecular non-covalent interactions.

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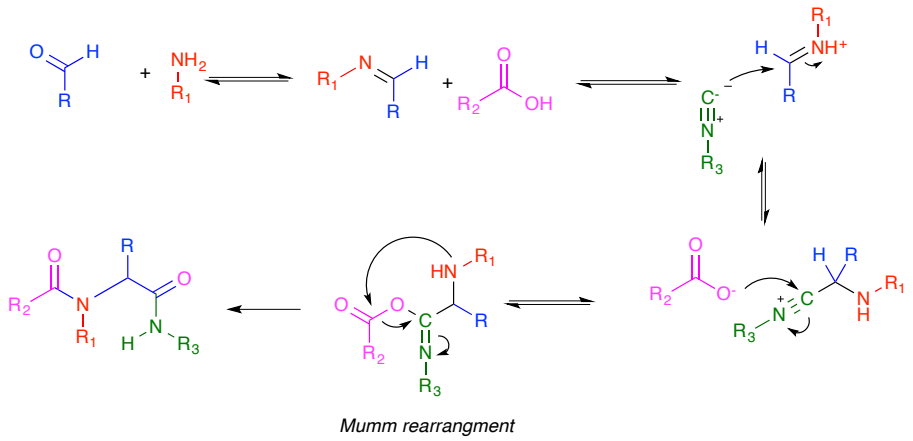
Chapter 3. Synthesis of methyl substituted all-cis tetrafluorocyclohexane aldehydes and use in Ugi multicomponent reactions.

3.1. Introduction.

Following on from the work presented in Chapter 2, the stereoselective synthesis of a new 1-methyl substituted 2,3,5,6-all-*cis*-tetrafluorocyclohexane motif for use in library preparation was undertaken.[1–4] A key design feature of this new all-*cis*-tetrafluoro motif is the replacement of the problematic α-acyl hydrogen with a methyl group, generating a motif stable to hydrogen fluoride elimination. Use of such tetrafluorocyclohexane compounds to generate peptidomimetics would provide novel candidates for bioactivity screening programs. One of the most efficient methods to generate peptidomimetic compounds is through an Ugi multicomponent reaction. This protocol was named after Ivar Karl Ugi who reported the reaction in 1959.[5,6] The classic Ugi reaction involves four components (4-UCR, Ugi four-component reaction), comprising of an amine, an isocyanide, a carboxylic acid and a ketone or aldehyde. This combination results in an α-aminoacyl amide product as illustrated on Scheme 3.1. An attractive feature of this approach is that it generates molecular complexity in a one-pot reaction with high yields and good selectivity. The U-4CR is particularly versatile for diversity synthesis as a wide range of reactants are available.[5–7]



Scheme 3.1: Ugi four component reaction mechanism

The mechanism of the U-4CR reaction is shown in Scheme 3.1 and involves the initial condensation of the amine with an aldehyde, generating an imine intermediate.[8] This is followed by addition of the isocyanide carbon to the imine and then attack by the carboxylic

acid (Scheme 3.1). The final step involves the rearrangement of the acyl isoamide to form the α-aminoacyl amide product, also known as a *Mumm* rearrangment.[8,9]

In recent years, this reaction, along with related variants such as the Passerini three component reaction (P-3CR) and the Danishefsky two component reaction (D-2CR), have become widely used in the pharmaceutical industry in order to develop chemical librarieso f compounds with structural characteristics to natural peptides. [7,10–12]

3.2. Aims and objectives.

All-*cis*-1,2,4,5-tetrafluorocyclohexane derivatives offer a new motif for the pharmaceutical industry, which has no obvious analogue or counterpart. It became an aim of this research to incorporate this motif into more complex structural frameworks. With this in mind, the initial target here was all-*cis*-1,2,4,5-tetrafluorocyclohexane alcohol **3.9.** This could then be oxidised to the analogous aldehyde (**3.10**) for inclusion in 4-UCR (Figure 3.1). A synthetic route was developed, which lead to two diastereoisomers of the tetrafluorocyclohexane alcohol, **3.9.a** and **3.9.b** (Figure 3.1).[4] Several approaches were explored in an effort to increase both the yields and stereoselectivity of these compounds (Sections 3.5 and 3.6).

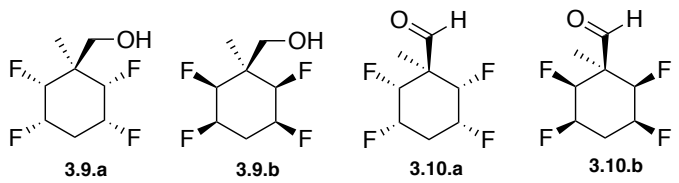


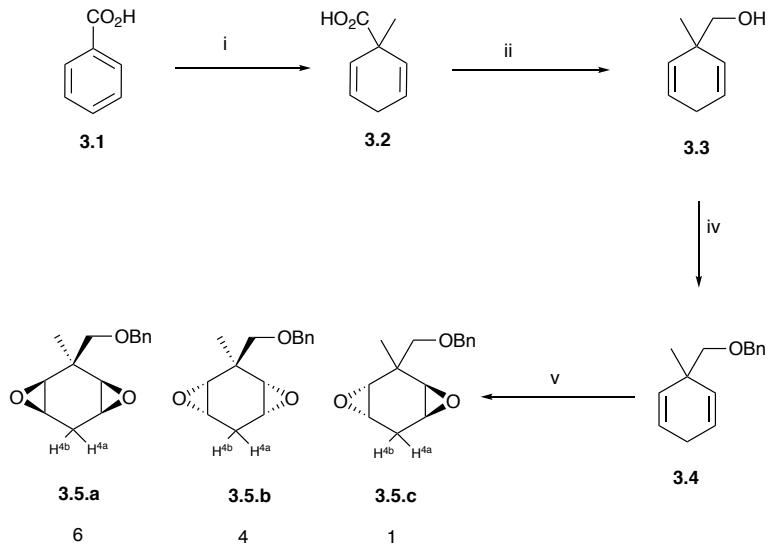
Figure 3.1: Targets, all-*syn*-tetrafluorocyclohexane aldehyde (3.10.a and 3.10.b) and alcohols (3.9.a and 3.9.b)

3.3. Synthesis of tetrafluorocyclohexane aldehyde.

3.3.1. Route towards tetrafluoro aldehyde.

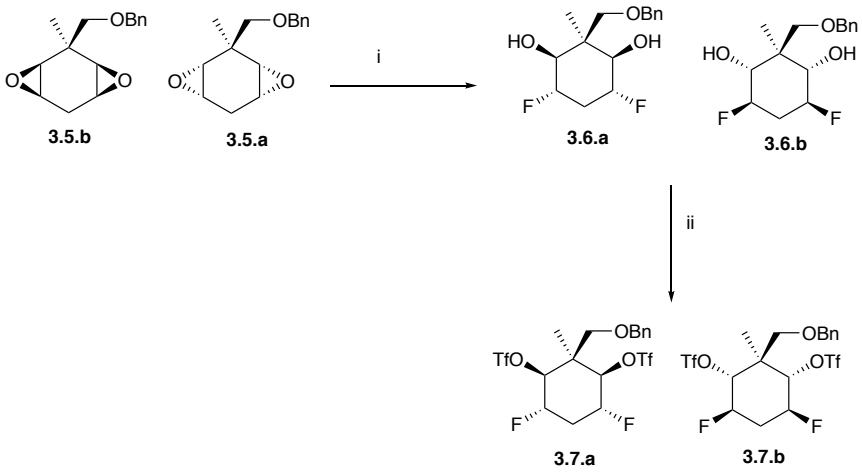
The synthesis began from an established protocol of the benzoic acid Birch reduction in liquid ammonia, accompanied by *in situ* methylation to afford carboxylic acid (**3.2**).[4,13] Reduction of carboxylic acid **3.2** with $LiAlH_4$ gave alcohol **3.3** in good yield (Scheme 3.3).[14] Protection of the primary alcohol (**3.3**) with benzyl bromide afforded ether **3.4** (80% yield), which was then epoxidised using an excess of *m*CPBA.[15,16] This reaction gave three diastereoisomers of the diepoxide **3.5**, *cis* (**3.5.a** and **3.5.b**) and *trans* (**3.5.c**) in ratio of 6:4:1.[4]

Diepoxides (**3.5.a**) and (**3.5.b**) were co-purified as the major products of this reaction (70% yield) and the *trans*-diepoxide **3.5.c** was isolated separately as a minor product (7% yield) (Scheme 3.3, step v). The configuration of each of these epoxides was determined by ^1H NMR spectroscopy. The *cis*-diepoxides (**3.5.a** and **3.5.b**) could be differentiated from the *trans* through the methylene hydrogen atoms 4a and 4b (Scheme 3.2). In the *trans*-diastereoisomer both hydrogens are in similar environment and appear as an unresolved signal (δ 2.30 ppm), whereas for the *cis*-diepoxides (**3.5.a** and **3.5.b**) these protons are non equivalent and they resolve into a pair of multiplets (δ 2.77 ppm and δ 2.24 ppm).



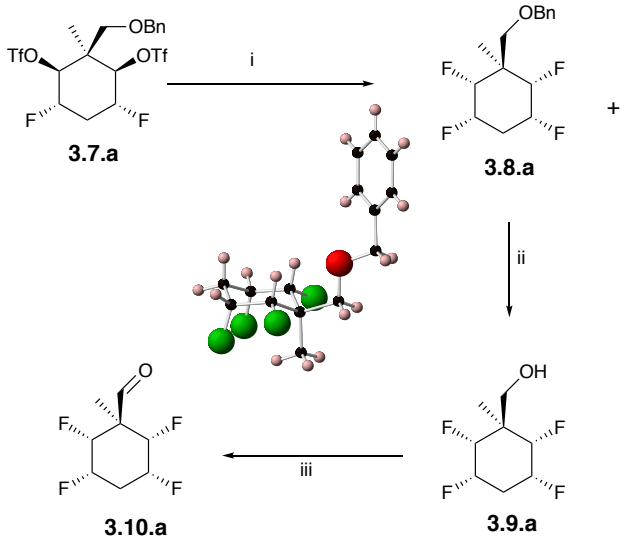
Scheme 3.2: (i) Li,NH_3, MeI, THF, 12 h, -78 °C, 91%; (ii) $LiAlH_4$, THF, 2 h, 0 °C, 83%; (iii) NaH, BnBr, THF 12 h rt, 80%; (iv) *m*CPBA, DCM, 14 h, 0 °C, 70% (3.5.a & 3.5.b), 7% (3.5.c)

Treatment of the diepoxide mixture **3.5.a** and **3.5.b** with $Et_3N.3HF$ at 140 °C, proved to be the most effective conditions for epoxide opening of these compounds. Reaction with the more acidic Olah's reagent (HF·pyridine) or DeoxyFluor was less suitable and in each case produced unwanted side products.[17,18]



Scheme 3.3: (i) $Et_3N.3HF$, 28 h, 140 °C; (ii) Tf_2O, pyridine, 1 h, 0 °C, 48 h, rt, 30% (3.7.a), 28% (3.7.b)

As a result, full conversion to difluoro diols **3.6.a** and **3.6.b** was achieved with $Et_3N.3HF$, as no starting material was observed after an 18 h reaction time (^1H NMR) and two new products were clearly evident by ^{19}F NMR (δ -183.66, -190.65 ppm), suggesting the formation of **3.6.a** and **3.6.b** (Scheme 3.3).



Scheme 3.4: (i) $Et_3N.3HF$, 42 h, 110 °C, 35%; (ii) 10% Pd/C, H_2, EtOAc, 18 h, rt, 55%; (iii) IBX, DMSO, 18 h, rt, 90%

Treatment of this product mixture with triflic anhydride in pyridine at 0 °C, after chromatography resulted in two diastereoisomeric

triflates in yields of 30% (**3.7.a**) and 28% (**3.7.b**) respectively (Scheme 3.4).Diastereoisomer **3.7.a** was then reacted with $Et_3N.3HF$ under forcing conditions (110 °C) to give tetrafluorocyclohexane **3.8.a** only after 3 days, as shorter reaction times gave poor conversions. This isomer has all of the fluorine atoms *syn* to the methyl group. The structure and stereochemistry of product **3.8.a** was confirmed by ^{19}F, ^{13}C, ^{1}H NMR and X-ray crystallography (Scheme 3.4).

O-Debenzylation of **3.8.a** was then performed (10% $Pd/C/H_2$), which generated alcohol **3.9.a**, as illustrated in Scheme 3.4.[19] This alcohol was also found to be a crystalline solid and its X-ray structure along with its ^{1}H NMR spectrum is shown in Figure 3.2.

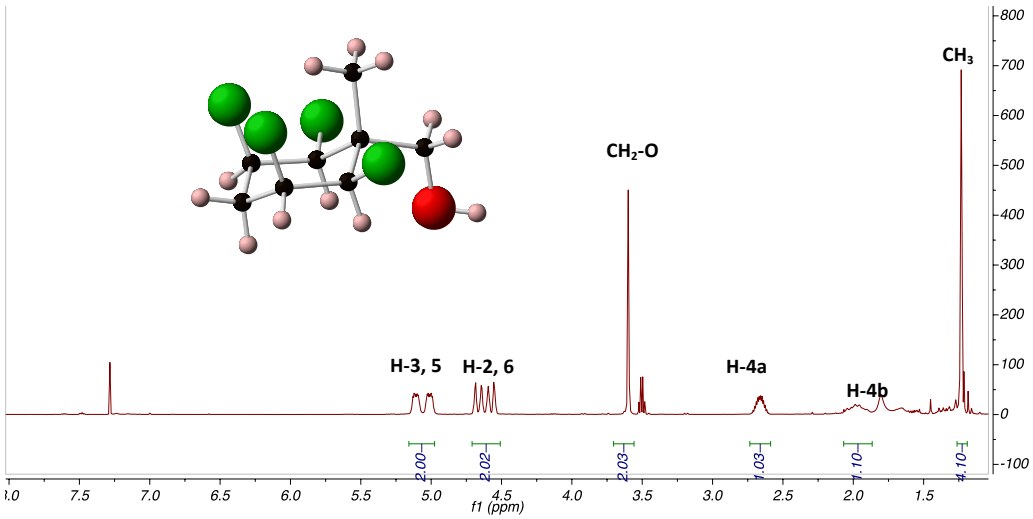


Figure 3.2: ^{1}H NMR (500 MHz, $CDCl_3$) and X-ray structure of 3.9.a.

A similar procedure was carried out on diastereoisomer **3.7.b**, to generate **3.8.b** (36%), which has its four fluorine atoms *syn* to each other but *anti* to the methyl group. As before, *O*-debenzylation using 10% palladium on carbon generated alcohol **3.9.b** (59%) (Scheme 3.5). The X-ray structures of benzyl ether (**3.8.b**) and the corresponding deprotected alcohol (**3.9.b**) are shown in Figure 3.3.[19]

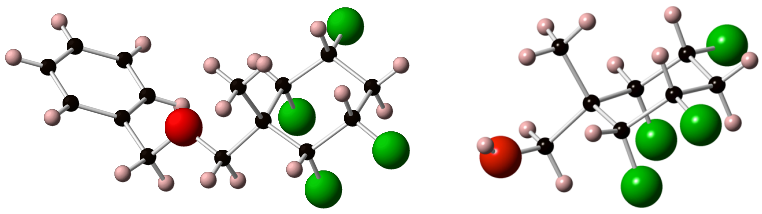
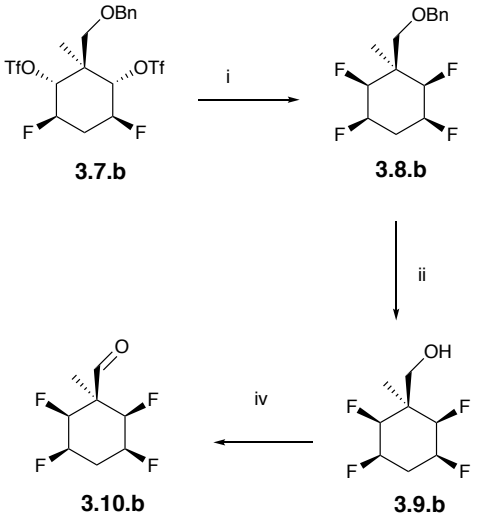


Figure 3.3: X-ray structures of all-*syn*-tetrafluorocyclohexanes (3.8.b) and (3.9.b).

Finally, the target aldehydes **3.10.a** and **3.10.b** were prepared by oxidation of primary alcohols **3.9.a** and **3.9.b**. This oxidation was achieved using IBX in DMSO as a solvent, yielding aldehydes **3.10.a** (90%) and **3.10.b** (68%) respectively (Scheme 3.4 and 3.5). [20,21]



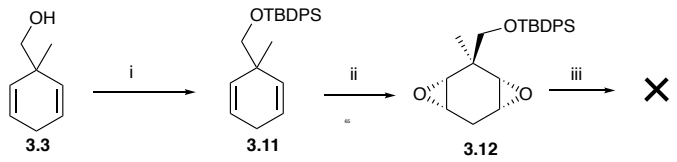
Scheme 3.5: (i) $Et_3N.3HF$, 42 h, 110 °C, 36%; (ii) 10% Pd/C, H_2, EtOAc, 18 h, rt, 59%; (iii) IBX, DMSO, 18 h, rt, 68%.

The yields for the fluorination reactions of difluoro ditriflates **3.7.a** and **3.7.b** were low, which was found to be due to the reactivity of the benzyl ether and possible fluoride elimination from the ring. It was therefore decided to focus on improving these yields through modification of the synthesis, as described in sections 3.5-3.6 below.

3.3.2. Optimisation of synthetic pathway: Protection of alcohol.

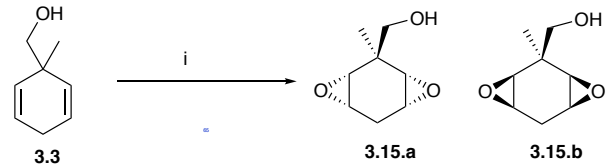
The poor diastereoselectivity during the diepoxidation process added complexity (Scheme 3.2, step v). Epoxidation of benzyl ether **3.4** gave all three possible diastereoisomers (**3.5.a**, **3.5.b** and **3.5.c** in a ratio of 6:4:1). It was not immediately possible to determine, which of the *cis*-diepoxides was *syn* and *anti* to the methyl group, due to the similarity of the C-4 methylene proton environments observed by ^{1}H NMR. Both *cis*-diepoxides eluted and could not be separated by conventional chromatography. In order to increase the diastereoselectivity during the epoxidation stage, a different protecting group was explored, in an effort better differentiate each face of the cyclohexadiene ring.

tert-Butyldiphenylsilyl (TBDPS) was initially chosen as a protecting group due to its large size.[22] Favourable diepoxidation of **3.11** resulted in only one diastereoisomer (**3.12**), in a yield of 69% (Scheme 3.6). This was isolated by chromatography and explored in subsequent fluorination reactions. However treatment with Et_3.HF gave a complex product mixture. Clearly the silyl protecting group is cleaved prior to epoxide ring opening, resulting in a wide range of side products. It was therefore decided to explore other strategies to increase the diastereoselectivity of the diepoxidation.



Scheme 3.6: (i) 1.2 eq. TBDPSCl, Imidazole, I_2, THF, 12 h, rt, 65%; (ii) *3* eq. *m*CPBA, DCM, 14 h, 0°C (69%); (iii) $Et_3N.3HF$, 14 h, 130 °C.

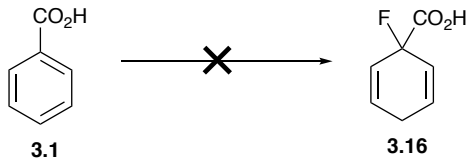
Epoxidation was also investigated on the free alcohol to explore co-cordination by *m*CPBA (Henbest effect), however the resulting reaction did not present any advantage in terms of diastereoselectivity.[23] ^{1}H NMR analysis of the product mixture showed equal proportions (6: 7.5) of *syn* to *anti* diastereoisomers of the *cis*-diepoxides (**3.15.a**, **3.15.b**). This mixture proved impossible to resolve by flash chromatography (Scheme 3.7).



Scheme 3.7: (i) *3* eq. *m*CPBA, DCM, 14 h, 0°C

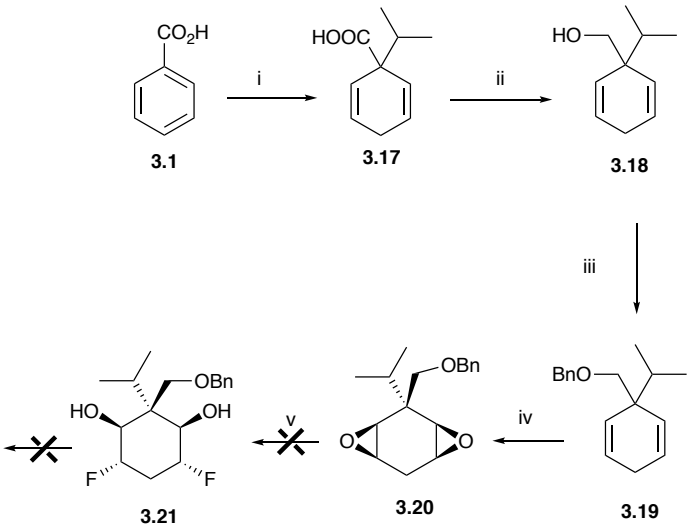
3.3.3. Optimisation of synthetic pathway: Substitution of the methyl group.

In a continuing effort to improve diastereoselectivity during diepoxidation, substitution of the methyl group on the cyclohexadiene ring of **3.4** with an alternative directing group was explored. In the first instance fluorination was investigated. Its high electronegativity was anticipated to direct the attack of *m*CPBA to the opposite face of the double bonds. In our hands quenching the 2,5-cyclohexadiene anion, formed from the Birch reduction, with Selectfluor did not however afford the desired fluorocyclohexadiene (Scheme 3.8).



Scheme 3.8: Li,NH_3, 2.5 eq. Selectfluor, THF, 3 h, -78 °C

Substitution with an isopropyl group was then explored, following a literature procedure to obtain cyclohexadiene carboxylic acid **3.17**.[13,24,25] Carboxylic acid **3.17** was then reduced to alcohol **3.18** with $LiAlH_4$, and the alcohol was treated with benzyl bromide to generate ether **3.19**. Diepoxidation of **3.19** showed good selectivity, resulting in only one diepoxide diastereoisomer **3.20** in 75% yield (Scheme 3.9).



Scheme 3.9: (i) Li,NH_3, $(CH_3)_2CHI$, THF, 12 h, -78 °C, 76%; (ii) $LiAlH_4$, THF, 2 h, 0 °C, 85%; (iii) NaH, BnBr, THF, 12 h, rt, 80%; (iv) *m*CPBA, 14 h, DCM, 0 °C, 75%; (ii) $Et_3N.3HF$, 14 h, 130 °C; Tf_2O, pyridine, DCM, 1 h, 0 °C, 48 h, rt,

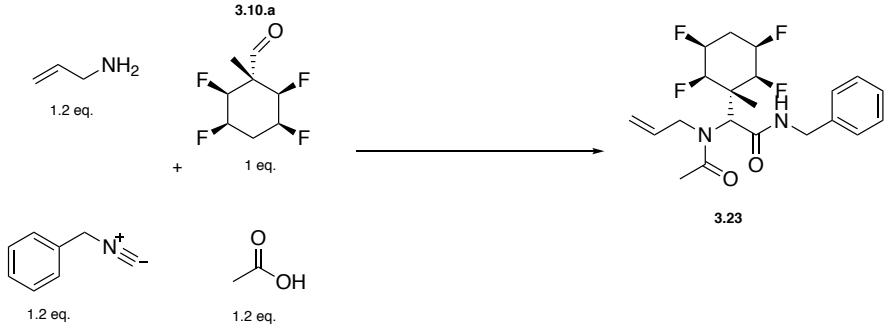
The product stereoisomer was assumed to locate the epoxide oxygens *anti* to the isopropyl group (Scheme 3.9). Following this, hydrofluorination of diepoxide **3.20** was explored (step v, scheme 3.9). Conversions were very low and attempts to purify only minor fluorinated products were unsuccessful. In an attempt to progress these minor components, the synthesis was advanced further and the crude product was treated directly with triflic anhydride. However this proved unsuccessful in identifying any isolatable products despite the high diastereoselectivity of the epoxidation (Scheme 3.9). Presumably the steric impact of the isopropyl group rendered diepoxide **3.20**, extremely unreactive and it was therefore decided to terminate this particular route.

3.3.3. Summary.

Target aldehydes **3.10.a** and **3.10.b** were prepared as substituents for use in Ugi multicomponent reactions. The most notable problem encountered during the synthesis was the inefficiency of the second fluorination step on the triflated difluorohydrins **3.7.a** and **3.7.b** and the selectivity of the epoxidation step. Various attempts were made to provide an alternate, higher yielding, synthesis towards the target aldehydes **3.10.a** and **3.10.b**, however this did not result in a more efficient synthetic route.

3.4. Incorporation of tetrafluorocyclohexane aldehyde into Ugi four-component reactions.

The application of the tetrafluoro aldehydes **3.10.a** and **3.10.b** in Ugi four-component reactions was explored. To begin with, an Ugi reaction was performed with commonly used components, comprising of: acetic acid, allylamine and benzyl isocyanide (Scheme 3.10). All four components were mixed together and the progress of the reaction was monitored by TLC.



Scheme 3.10: First exploration of Ugi four multicomponent reaction using tetrafluoro aldehyde 3.10a; DCM, 18 h at rt, 15 h at 35◦C, 58%.

Due to the persistent presence of the aldehyde in the reaction mixture, after 5 h at room temperature, it proved expedient to increase the temperature to 35 °C, below the boiling point of any of the reagents (allylamine, 53°C).

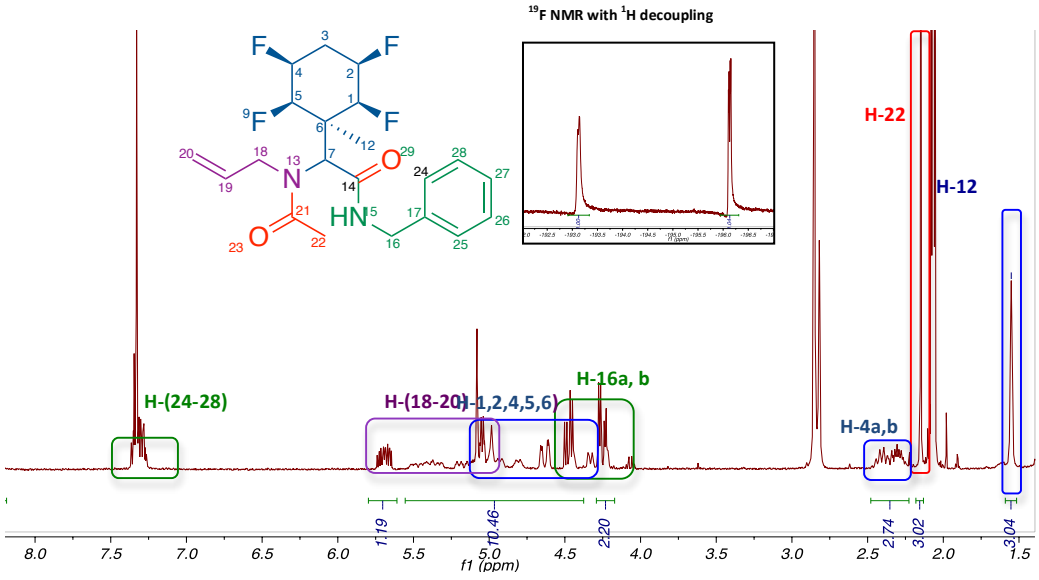
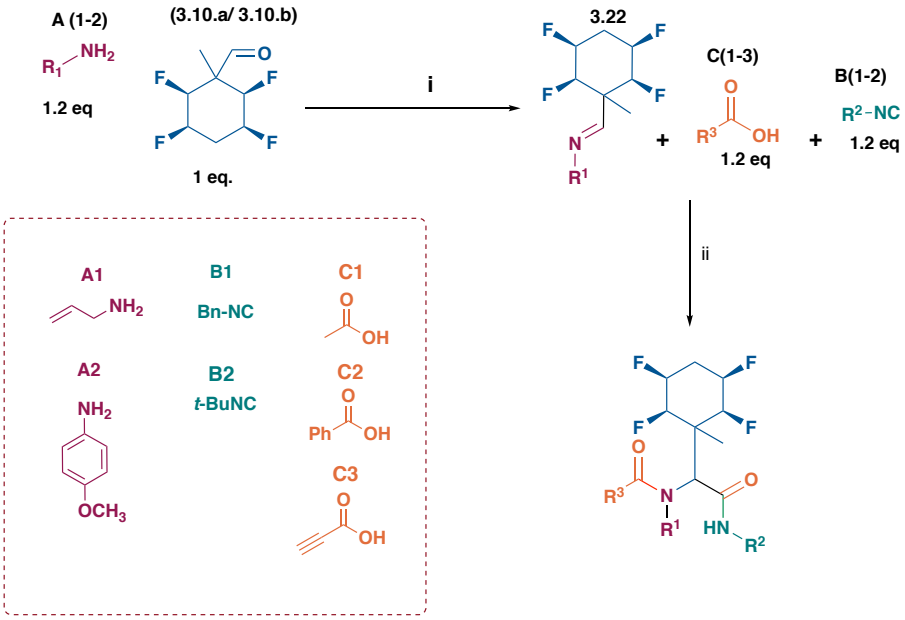


Figure 3.4: ^{1}H NMR (500 MHz, $CDCl_3$), ^{19}F NMR (476 MHz, $CDCl_3$) of compound 3.23.

Although a small amount of starting material **3.10.a** was recovered (16%) after a further 18 h reaction time, the anticipated amide **3.23** was obtained in 58% yield. The structure of the product was fully characterised (Figure 3.4) and was confirmed by X-ray crystallography (Figure 3.5).

In order to increase the conversion of the aldehyde in the U-4CC reaction, the reaction was modified by pre-combining amine with aldehyde to form the corresponding imine, prior to the addition of the other substrates.



Scheme 3.11: General Ugi procedure involving aldehydes 3.10.a and 3.10.b and a range of amines (A1-2), isocyanides (B1-2) and carboxylic acids (C1-3); (i) DCM/MeOH, $MgSO_4$, 16 h, 35 °C; (ii) DCM/MeOH, 24 h, 35 °C.

The general reaction is represented in Scheme 3.11, and begins with the condensation of the tetrafluoro aldehyde **3.10.a**/**3.10.b** with an amine **A1**/**A2** to form the anticipated imine **3.22**. The complete condensation was followed by TLC and ^{1}H NMR where after 18 hours there was no longer any observable aldehyde peak (CHO) (9.49 ppm for aldehyde **3.10.a** and 9.98 ppm for **3.10.b**). The reaction then proceeds with the addition of the isocyanide and carboxylic acids.

Using both diastereoisomers of tetrafluoro aldehydes, **3.10.a** and **3.10.b** along with a range of amines (**A1-2**), isocyanides (**B1-2**) and carboxylic acids (**C1-3**), a series of reactions were conducted to generate a small chemical library of peptidomimetics **3.23**-**3.40**, each carrying the tetrafluorocyclohexyl ring motif (Scheme 3.11, Table 3.1 and 3.2). These compounds are all racemic as a new stereogenic centre is generated.

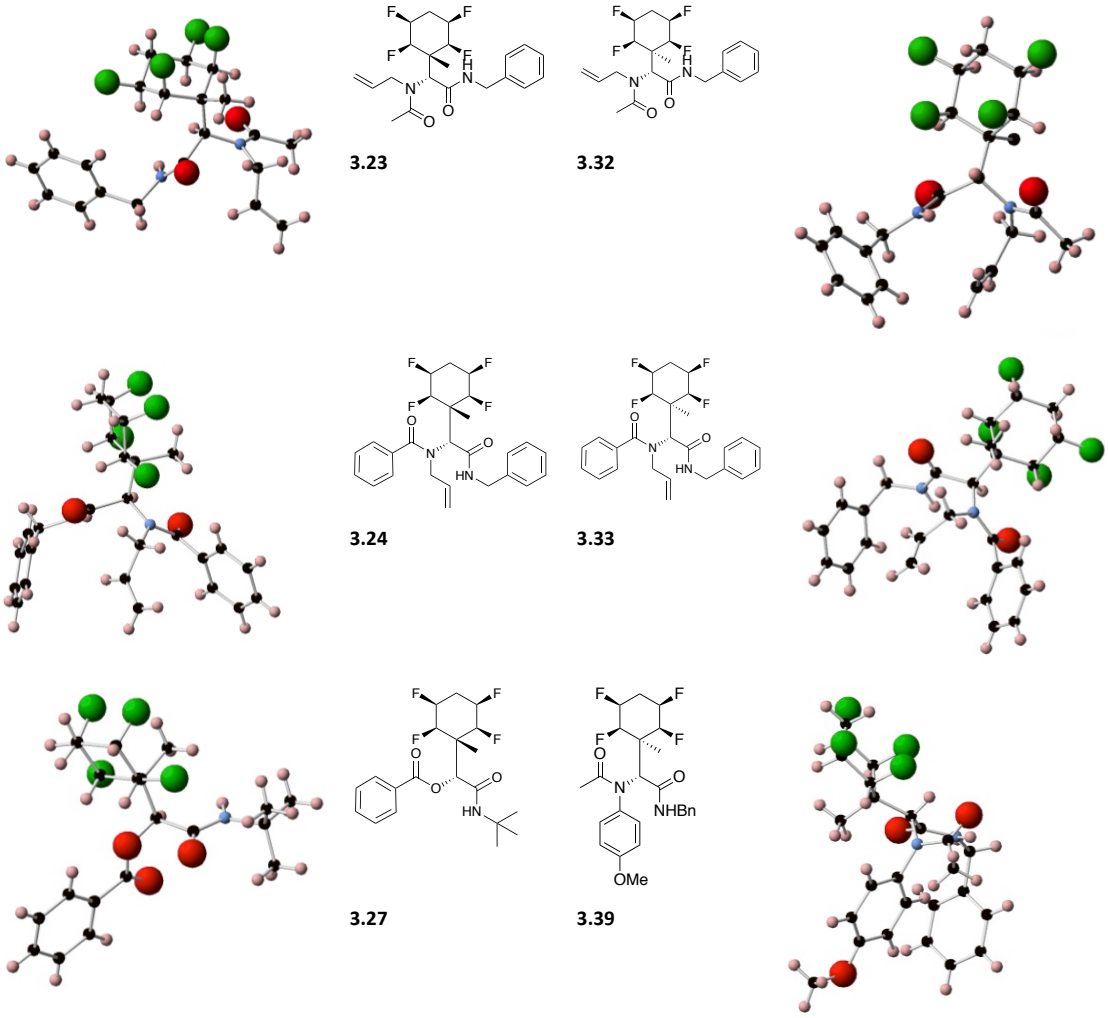
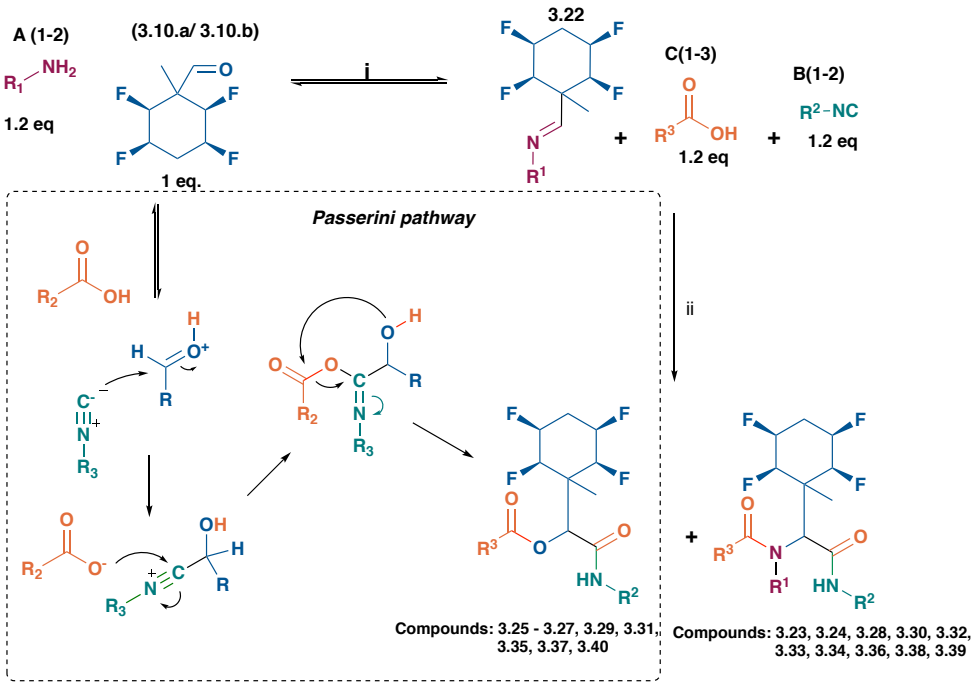


Figure 3.5: X-ray structures of a selected α-aminoacyl amides 3.22, 3.31, 3.32, 3.38, which derive from reaction entries 1,2,8,9 and 14 in Table 1, and of the Passerini by-product 3.26 from reaction entry 3 of Table 3.1.

While a number of compounds were obtained by the classic route using the U-4CC reaction, others emerged as a result of the Passerini reaction (Table 3.1 and 3.2), through direct reaction of the aldehyde with isocyanides and carboxylic acids (Scheme 3.11). [10,10,26] The crystal structures of Ugi products **3.23**, **3.24, 3.32, 3.33 and 3.39,** and a Passerini α-hydroxy carboxamide product **3.27** are shown of Figure 3.5. In each case, compensating enantiomers of these racemic products are obvious in the unit cell of each crystal structure.

During this synthetic study, the majority of combinations of the four components were found to produce both U-4CC and Passerini type products. Since the modified U-4CR procedure towards the generation of these peptidomimetics ensured an initial full conversion of the amine and aldehyde to an imine, it can be assumed that the imine is in

equilibrium with the aldehyde and amine and this aldehyde subsequently reacts via the Passerini mechanism in order to form α-acyloxy amide product (Scheme 3.12).



Scheme 3.12: General Ugi U-4CC reaction, showing alternative Passerini pathway.

The proportions of the U-4CC and Passerini type products were found to depend on stereoelectronic factors, acidity and solvent effects (see Table 3.1). Steric effects were also observed with respect to the substitution of the isocyanide component. For instance, in the reaction where benzyl isocyanide is used along with aldehyde **3.10.a** or **3.10.b**, only the U-4CC type products (**3.23** and **3.32)** are observed. However only Passerini type product (**3.26**) is detected when *tert*-butyl isocyanide is used in the reaction with aldehyde **3.10.a** and in reaction with aldehyde **3.10.b**, the ratio of Ugi (**3.34**) to Passerini (**3.35**) products is 1:2 (Table 3.1).

The pKa of the carboxylic acids used was also found to have a significant influence on the resulting product (Tables 3.1 and 3.2). The more acidic the carboxylic acid the more the ratio was biased in favor of the Passerini type product. Only U-4CC product **3.23** was observed when acetic acid (pKa= 4.8) is used, while the use of benzoic acid (pKa= 4.2) gave the **3.24** (U-4CC type) and **3.25** (Passerini type) products in a 1:2 ratio (Table 3.1). Substituting benzoic acid with the more acidic 2-butynoic acid (pKa= 2.6), elevated the ratio to 1:2.5 in favor of the Passerini product **3.29** (Table 3.1).

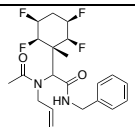
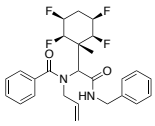
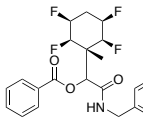
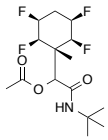
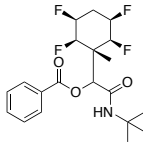
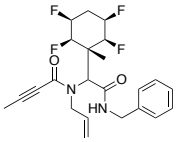
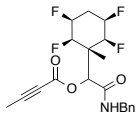
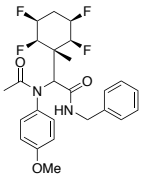
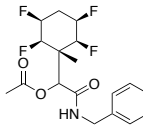
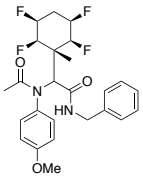
Entry	R^1CNH_2	R^2CN	R^3COOH	Conditions (time, temp, solvent)	Ugi (1) (yield)	Passerini (2) (yield)	Ratio (1: 2)
1	**A1**	**B1**	**C1**	40 h, 35 °C, DCM	 **3.23** (58%)	N/A	-
2	**A1**	**B1**	**C2**	40 h, 35 °C, DCM	 **3.24** (25%)	 **3.25** (20%)	2:1
3	**A1**	**B2**	**C1**	40 h, 35 °C, DCM	N/A	 **3.26** (82%)	-
4	**A1**	**B2**	**C2**	40 h, 35 °C, DCM	N/A	 **3.27** (79%)	-
5	**A1**	**B1**	**C3**	40 h, 35 °C, DCM	 **3.28** (22%)	 **3.29** (30%)	1:2.5
6	**A2**	**B1**	**C1**	40 h, 35 °C, DCM	 **3.30** (25%)	 **3.31** (37%)	4:5
7	**A2**	**B1**	**C1**	40 h, 35 °C, MeOH	 **3.30** (53%)	N/A	

Table 3.1: Compounds produced using aldehyde 3.10.a in U-4CC reactions

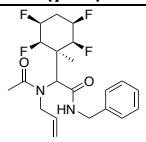
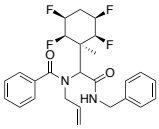
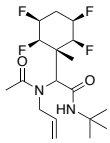
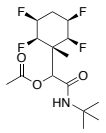
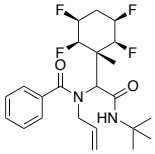
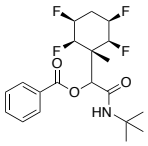
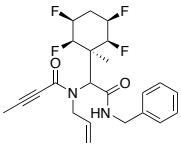
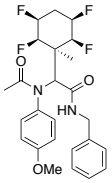
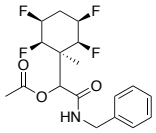
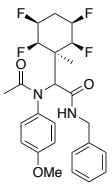
	R^1CNH_2	R^2CN	R^3COOH	Conditions (time, temp, solvent)	Ugi (1) (yield)	Passerini (2) (yield)	Ratio (1: 2)
8	**A1**	**B1**	**C1**	40 h, 35 °C, DCM	 **3.32** (72%)	N/A	-
9	**A1**	**B1**	**C2**	40 h, 35 °C, DCM	 **3.33** (80%)	N/A	-
10	**A1**	**B2**	**C1**	40 h, 35 °C, DCM	 **3.34** (26%)	 **3.35**(41%)	1:2
11	**A1**	**B2**	**C2**	40 h, 35 °C, DCM	 **3.36** (18%)	 **3.37** (25%)	1:2
12	**A1**	**B1**	**C3**	40 h, 35 °C, DCM	 **3.38** (46%)	N/A	-
13	**A2**	**B1**	**C1**	40 h, 35 °C, DCM	 **3.39**	 **3.40** (43%)	1:8
14	**A2**	**B1**	**C1**	40 h, 35 °C, MeOH	 **3.39** (46%)	N/A	-

Table 3.2: Compounds produced using aldehyde 3.10.b in U-4CC reactions

Replacing allylamine for *p*-anisidine resulted in Passerini products **3.31** (using aldehyde **3.10.a**) and **3.40** (aldehyde **3.10.b**) as major products, while using dichloromethane as a solvent. The ratio changed dramatically once dichloromethane was substituted with methanol, producing Ugi products **3.30** and **3.39** (Table 3.1 and 3.2). Different diastereoisomers of aldehydes (**3.10.a** and **3.10.b**) with the same set of carboxylic acids, isonitriles and amines also resulted in different in Ugi/Passerini ratios. As a general trend, U-4CC type product is more favoured using aldehyde **3.10.b** (with the aldehyde moiety being on the fluorous side of the cyclohexane ring), than aldehyde **3.10.a.** The reason for this tendency is not clear.

A comment regarding the $^{19}F\{^{1}H\}$-NMR spectra of a number of these compounds is merited. Aldehydes **3.10.a** and **3.10.b**, each have two sets of broad peaks with equivalent fluorines. However, the multicomponent products differ due to the formation of a new stereogenic center. Now the two sets of originally equivalent fluorines become diastereotopic and all four fluorine atoms become chemically nonequivalent, which in some cases results in the resolution of four separate signals in the $^{19}F\{^{1}H\}$-NMR spectra (Figure 3.6).

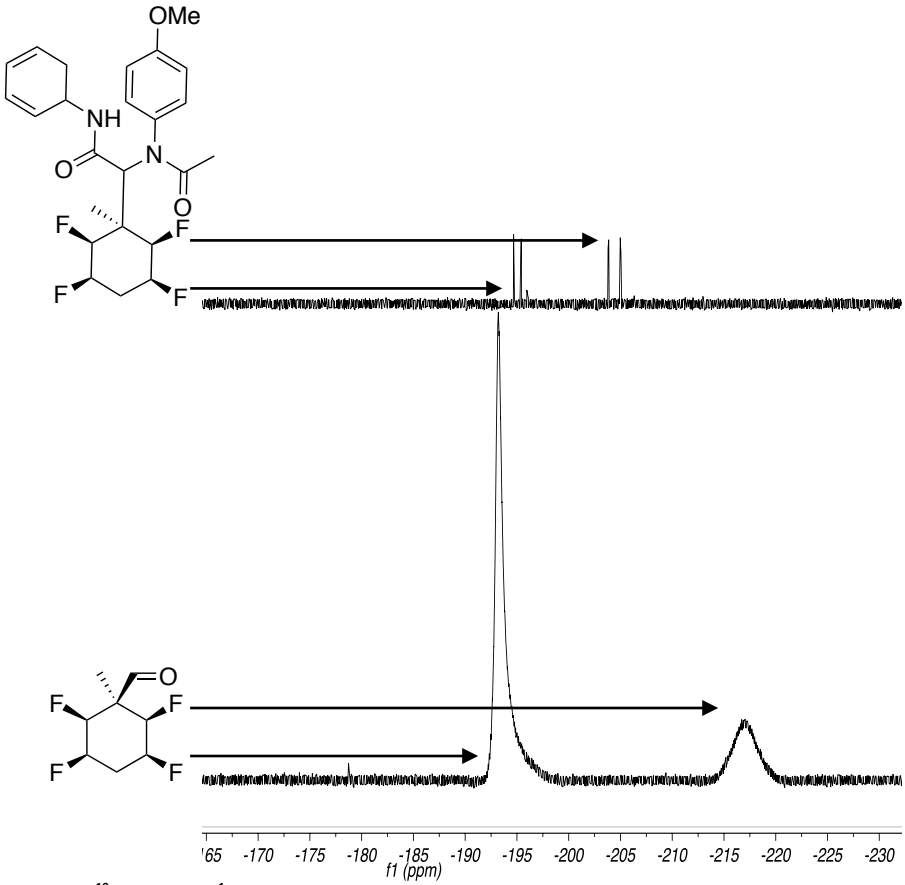


Figure 3.6: ^{19}F NMR with ^{1}H decoupling (376 MHz, $CDCl_3$) of α-aminoacyl amide 3.39 (top) and tetrafluoro cyclohexane aldehyde 3.10.a.

3.5. Conclusion.

In conclusion, two diastereoisomers of all-*cis*-2,3,5,6-tetrafluorocyclohexane aldehyde motifs were prepared through a nine-step route. These organofluorine motifs have been incorporated into U-4CC reactions, generating a small chemical library of fluorinated peptidomimetics. In total 10 α-aminoacyl amides and 8 α-acyloxy amides were prepared. This work has developed a foundation for the introduction of facially polarized all-*cis*-tetrafluorocyclohexane motifs into peptidomimetic scaffolds and these have the potential to be used for exploration in bioactivity screening programmes.

3.6. References.

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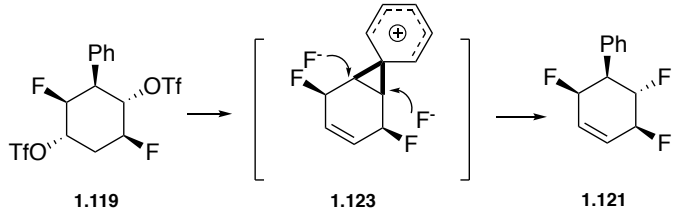
Chapter 4. The observation of phenonium rearrangements.

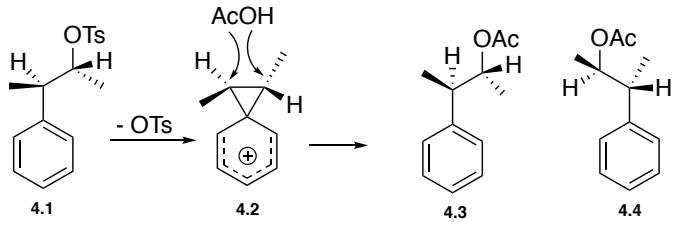
4.1. Introduction.

The synthesis of all-*cis*-phenyl-2, 3, 5, 6-tetrafluorocyclohexane **1.122** has provided the starting point for the production of a diverse library of compounds carrying a tetrafluoro cyclohexyl moiety with 'all-*cis*-fluorines', as described in Chapters 1 and 2.[1–5] However, as noted in Chapter 1 (Section 1.6), a major issue during these syntheses was the formation of the side product **1.121**, which arose through elimination followed by a phenonium ion rearrangement (Scheme 4.1).[3,4]



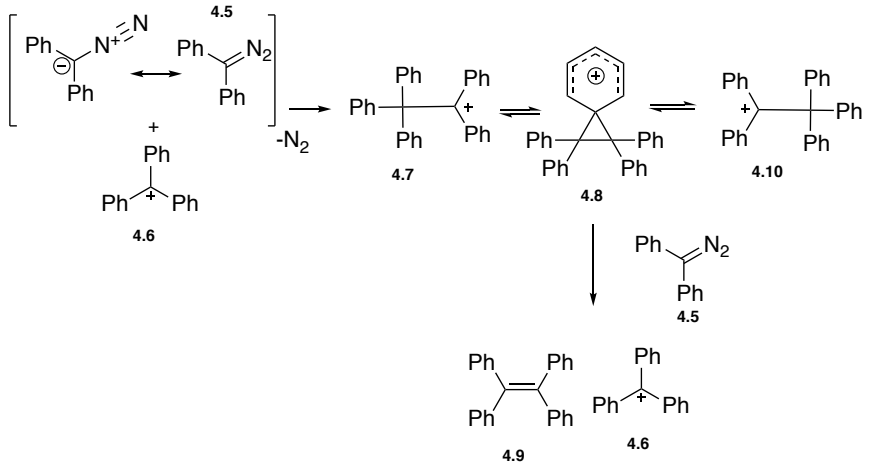
Scheme 4.1: Phenonium ion rearangment during synthesis towards all-*cis*-phenyl-2, 3, 5, 6-tetrafluorocyclohexane 1.122, Chapter 1.

In phenonium ion rearrangment reactions, an aryl group contributes to the delocalisation of a positive charge through the formation of a phenonium ion intermediate by neighboring group participation. These type of reactions have been thoroughly investigated in the past few decades.[6–8] Early reports of this rearrangements were detailed by Cram *et. al,* whereby the acetolysis of *p*-toluenesulfonate (**4.1**) resulted in an equimolar mixture of two major acetate products **4.3** and **4.4**, suggesting that the reaction proceeds through a phenonium ion intermediate **4.2** (Scheme 4.2).[9,10]



Scheme 4.2 Solvolysis of *p*-toluenesulfonate 4.11; Ac_2O/HOAc. (1:1), KAc, 70 °C, 30 h. [9,10]

It has also been shown by Olah *et.al* that the reaction of trityl cation **4.6** and diphenyl diazomethane **4.5** also involves phenonium ion neighbouring group participation.[11] Deuterium and ^{13}C labelling experiments established that the reaction proceeds through pentaphenylethyl (**4.7**), which undergoes a 1,2 phenyl exchange, forming intermediate **4.8** (Scheme 4.3).[11]



Scheme 4.3: Reaction of trityl cation 4.6 and diphenyl diazomethane 4.5; DCM, 1 h, rt.[11]

It was anticipated that the substitution of hydrogen at the benzylic position of all-*cis*-2, 3, 5, 6 tetrafluorophenylcyclohexane motif (Figure 4.1) with a methyl group would suppress any elimination side products formed and offer a more robust and stable building block. Chapter 3, describes the synthesis of such a motif, whereby during the Birch reduction of benzoic acid **3.1**, a methyl group was introduced by quenching with methyl iodide, forming methylated cyclohexene carboxyl acid derivative **3.2** (Figure 4.1).

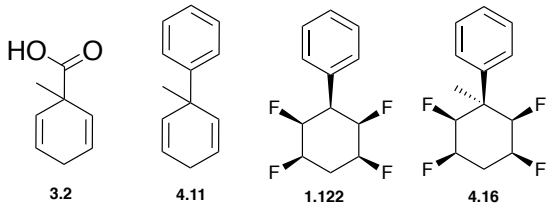


Figure 4.1: 1-Methylcyclohexa-2,5-diene-1-carboxylic acid (3.2), methylated phenyl cyclohexene (4.11), all-*cis*-2, 3, 5, 6 tetrafluorophenylcyclohexane (1.122), methylated all-*cis*-phenyl-2,3,5,6-tetrafluorocyclohexane (4.16)

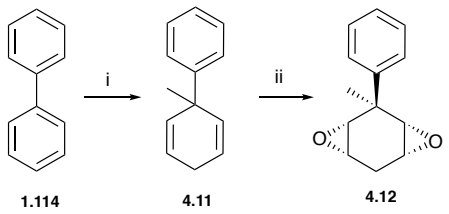
A problem with this methylated building block was the poor selectivity it exhibited during the epoxidation stage of the synthesis, which lead to two diepoxide diastereoisomers that proved impossible to separate by column chromatography (Chapter 3). Despite the positive effects of having a blocking alpha methyl group at the benzylic position, which provided stability to this all-*cis*-fluorinated cyclohexane motif, the resulting two diastereoisomers of the tetrafuoro cyclohexane motifs generated during the synthesis lead to difficult purifications and hence negatively affected the overall synthesis yields.

4.2. Aims and Objectives.

As part of an overall aim to improve and expand the structural diversity of the all-*cis* tetrafluorocyclohexane motif, it was decided to modify the synthetic procedure towards all-*cis*-phenyl-2,3,5,6-tetrafluorocyclohexane **1.122** (Figure 4.1). During the first step a methyl group will be introduced when quenching the Birch reduction to block the benzylic position (in a similar manner to the method used to acquire methylated cyclohexene **3.2** (Figure 4.1)**,** described in Chapter 3. This will then be followed by established cascade of the fluorination reactions towards synthesis of all-*cis*-phenyl-2,3,5,6-tetrafluorocyclohexane **1.122,** previously described in Chapter 1**,** which eventually lead to the methylated all-*cis*-phenyl-2,3,5,6-tetrafluorocyclohexane **4.16** (Figure 4.1) .

4.3. Results and Discussion.

Following a literature method, the synthesis of methylated all-*cis*-phenyl-2,3,5,6-tetrafluorocyclohexane **4.16** (Figure 4.1) began from the Birch reduction of biphenyl **1.114**. This included a treatment with liquid ammonia and lithium metal at -78 °C, followed by an *in situ* methyl iodide quench, to afford methylated cyclohexadiene **4.11** in excellent yield (Scheme 4.4). [12,13]



Scheme 4.4: (i) Li,NH_3, MeI, THF, 12 h, -78 °C, 95% (recovery); (ii) *m*CPBA, DCM, 2 h, 0 °C, 68%.

Epoxidation of diene **4.11** with an excess of *m*CPBA afforded *cis*-diepoxide **4.12**, the configuration of which was confirmed by X-ray crystallography. As anticipated, it was found to have both epoxides positioned on the opposite side of the ring from the phenyl group (Figure 4.2).[14,15]

The ring opening of diepoxide **4.12** with $Et_3N.3HF$ at 140 °C resulted in difluoro diols **4.13** and **4.14** in a 2.8:1 ratio as indicated by ^{19}F-NMR (Scheme 4.5).[16,17] Diols **4.13** and **4.14** could not be easily separated by chromatography, and hence only an analytical sample of each was isolated for characterisation.

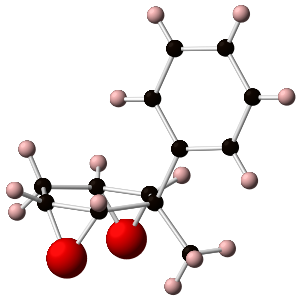
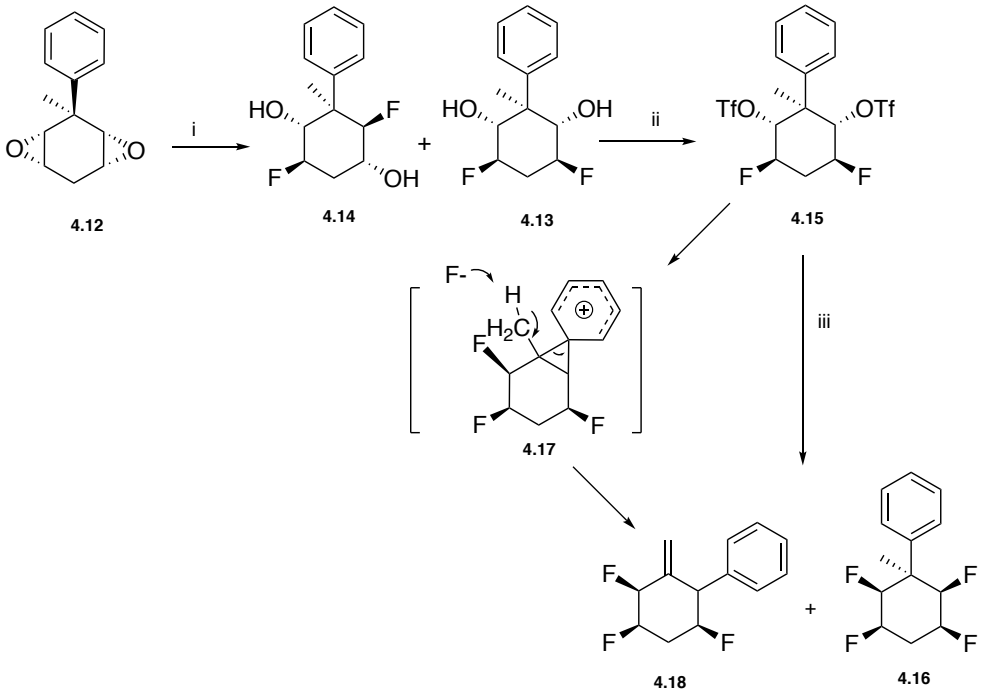


Figure 4.2: X-Ray structure of diepoxide 4.12

The mixture of **4.3** and **4.4** was subsequently treated with triflic anhydride in pyridine to afford triflate **4.15** as the major product (Scheme 4.5). No other significant products were observed. For instance there was no obvious trace of the presence of the triflate that arises from unsymmetrical difluoro diol **4.14**. This suggests that it undergoes various elimination reactions that lead to its decomposition.

Fluorination of difluoro ditriflate **4.15** with $Et_3N.3HF$ at 115 °C afforded trifluoro alkene **4.18** with an exo-methylene group (Scheme 4.5). This unexpected product was generated along with the anticipated all-*cis*-2, 3, 5, 6-tetrafluorocyclohexane **4.16**.



Scheme 4.5: (i) $Et_3N.3HF$, 18 h, 135°C; (i) Tf_2O, pyridine, 1 h, 0 °C, 18 h, rt; (iii) $Et_3N.3HF$, 36 h, 115 °C , 4.6 (17%) and 4.8 (23%)

.

Both products **4.16** and **4.18** were found to be crystalline solids and their structure and stereochemistry was confirmed through X-ray structure analysis, as shown in Figure 4.3. Formation of **4.18**, which contains an exocyclic double bond, clearly occurs via a phenonium ion, which results in the migration of the phenyl ring, concomitant with a mechanistically related E1 type elimination as illustrated on Scheme 4.5. [6,11,8]

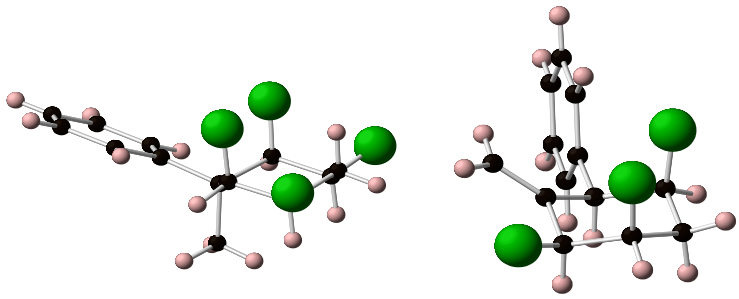
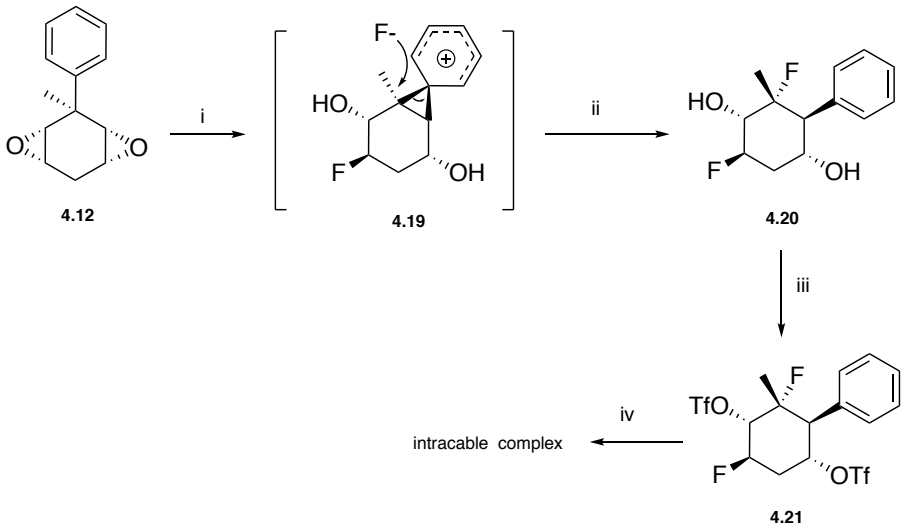


Figure 4.3: X-ray structures of products 4.16 (on the right) and 4.18 (on the left).

Since this fluorination route proved to be less successful than was anticipated, it was decided to explore an alternative fluorinating reagent in order to minimise unwanted side products. Treatment of diepoxide **4.12** with the more acidic Py.HF at -78 ° resulted in a complete conversion but to the unanticipated difluorodiol **4.20**, as illustrated in Scheme 4.6.



Scheme 4.6: Py.3HF, DCM, 18 h, rt (80%); (ii) Tf_2O, pyridine, DCM, 1 h, 0 °C, 6 h, rt (19%); (iii) Et_3N.3HF, 36 h, 115 °C.

The structure and stereochemistry of **4.20** was confirmed by X-ray crystallographic analysis, as shown in Figure 4.4. Two distinct fluorine peaks were observed in the ^{19}F NMR spectrum of **4.20**. Notably, the signal at -145 ppm is consistent with a fluorine atom positioned at a tertiary carbon (Figure 4.4).

The formation of **4.20** can be explained by acid catalyzed epoxide ring opening, which drives the formation of an unsymmetrical phenonium ion intermediate **4.19**, followed by nucleophilic attack by fluoride ion at the developing tertiary carbocation, as illustrated in Scheme 4.5. [3,4,8,10,11,17,18]

Reaction of **4.20** with triflic anhydride in pyridine at 0 °C gave the ditriflate **4.21.** However treatment of **4.21** with $Et_3N.3HF$ at 110 °C resulted in a complex mixture giving mostly de-fluorinated products, which could not be satisfactory characterised.

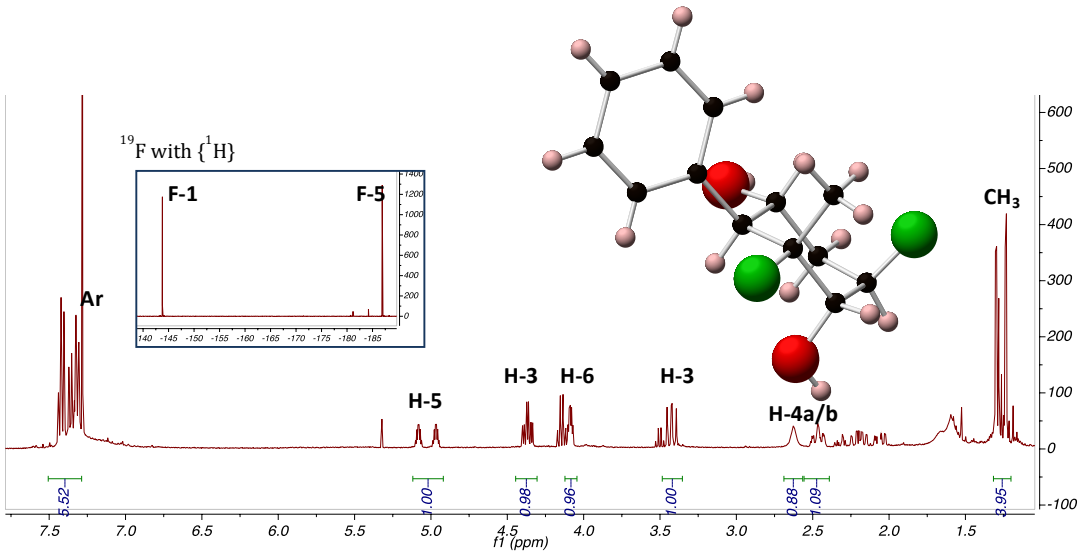


Figure 4.4: X-ray structure, ^{1}H NMR (500 MHz, $CDCl_3$); ^{19}F NMR (476 MHz, $CDCl_3$) of difluoro diol (4.20), a single compound of reaction of diepoxide (4.3) with Py.HF

4.3. Conclusion.

Although these synthetic pathways are not particularly useful for the preparation of a tetrafluorocyclohexyl motif, they reveal interesting mechanistic details, particularly concerning phenonium ion rearrangements. During these rearrangements the manner in which the aryl group is involved in neighbouring group participation is dependent upon the application of different deoxyfluorinating reagents. It follows from these findings, when using $Et_3N.3HF$ during the second fluorination step of the difluoro triflate **4.15** (Scheme 4.5), the fluoride ion deprotonates at the most acidic position resulting in trifluoro exo-methylene

product **4.18**. When the more acidic deoxoflurinating reagent Py.Hf is used (Scheme 4.6), following an aryl ring rearrangement, the fluoride ion in this case acts as a nucleophile, attacking at the most acidic position, furnishing compound **4.20**.

4.4. References.

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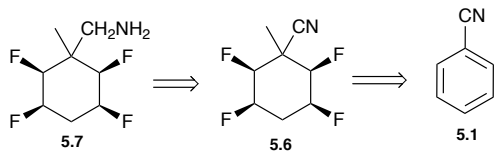
Chapter 5. Synthesis of amine building blocks.

5.1. Introduction.

The preparation of the all-*cis*-tetrafluorocyclohexane motif containing a methyl group at the benzylic position was described in Chapters 3 and 4. A continuing objective of this work is to provide access to a wider range of such building blocks for use by the broader research community, consequently the focus turned to the development of an amine building block.[1–6]

There were challenges encountered during the synthesis of all-*cis*-tetrafluorocyclohexane motifs (see Chapters 3 and 4). These included the selectivity exhibited during epoxidation reactions and the poor stability of these compounds. As a consequence it was decided not to further derivatise the already prepared tetrafluoro cyclohexane motifs, but rather to develop a new, analogous, pathway. The initial strategy involved selecting a starting material, which possessed a stable functional group that would not require protection/deprotection steps, and would direct and improve the epoxidation selectivity. Benzonitrile (**5.1**) was selected as a starting material to prepare tetrafluoro cyclohexane amine (**5.7**) (Scheme 5.1). The nitrile functional group has the advantage that it is relatively easily reduced to an amine and does not need protection. The installation of a methyl group at the benzylic position, similar to Chapters 3 and 4, was also necessary in order to guard against HF elimination.

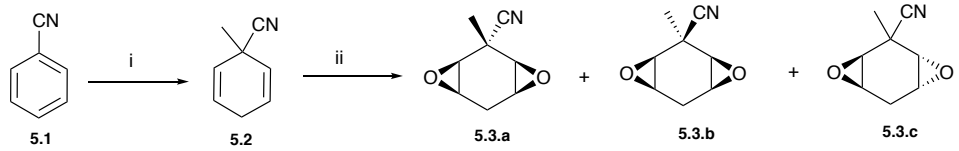


Scheme 5.1: Retrosynthetic route towards the all-*cis*-fluorinatedcyclohexane amino motif 5.7.

5.2. Route towards all-*cis*-2,3,5,6-tetrafluorocyclohexylamine.

A Birch reduction of benzonitrile **5.1** followed by *in situ* methylation with iodomethane was carried out following a previously reported procedure of cyclohexadiene **5.2**.[7,8] In comparison to the previous Birch reductions of biphenyl or benzoic acid, where conversion was high, the yields for this Birch reduction were considerably lower, and systematically showed an average of 30%.

Epoxidation of cyclohexadiene (**5.2**) with *m*CPBA resulted in the generation of three diepoxide diastereoisomers, in a ratio of 10: 15: 13 (**5.3.a**: **5.3.b**: **5.3.c**) (Scheme 5.2), one of which was the racemic *trans*-diepoxide (**5.3.c**). The other two diepoxides were the relative *syn* (**5.3.a**) and *anti* (**5.3.b**) products in relation to the nitrile functional group.[1,2,6,9,10] After column chromatography, diepoxide **5.3.a** was isolated in an 18% yield, however diepoxides **5.3.b** and **5.3.c** (35%) proved impossible to separate by this method, and hence both diastereoisomers were taken as a mixture to the next step of the synthesis.



Scheme 5.2: Reagents and conditions: a) Li (2.5 eq.), NH_3, *t*BuOH (1 eq.), MeI (2 eq.), 3 h, -78 °C, 18 h, rt, 31%; b) *m*CPBA (4.9 eq.), DCM, 48 h, 35 °C, 18% (8a), 35% (8b and 8c), ratio 8a /8b /8c: 10 /15 /13.

In an effort to improve the epoxidation selectivity, some other methods of epoxidation were explored, however neither reaction using vanadyl acetylacetonate with *tert*-butyl hydroperoxide, nor epoxidation with 2,2,2-trifluoroacetophenone and hydrogen peroxide resulted in any conversion (Table 5.1).[11,12]

Treatment of **5.3.a** with $Et_3N.3HF$ at 140 °C resulted in a full conversion to the ring opened fluorohydrin **5.4.a**. Only a single isomer could be detected by ^{19}F NMR. This product was then treated directly with triflic anhydride in pyridine, to generate ditriflate **5.5.a** in a 30% yield over two steps (Scheme 5.3). Finally, the tetrafluoro nitrile motif was generated through the reaction of triflate **5.5.a** using with an excess $Et_3N.3HF$ at 120 °C (Scheme 5.3).

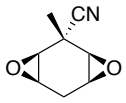
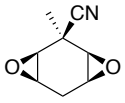
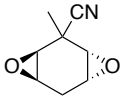
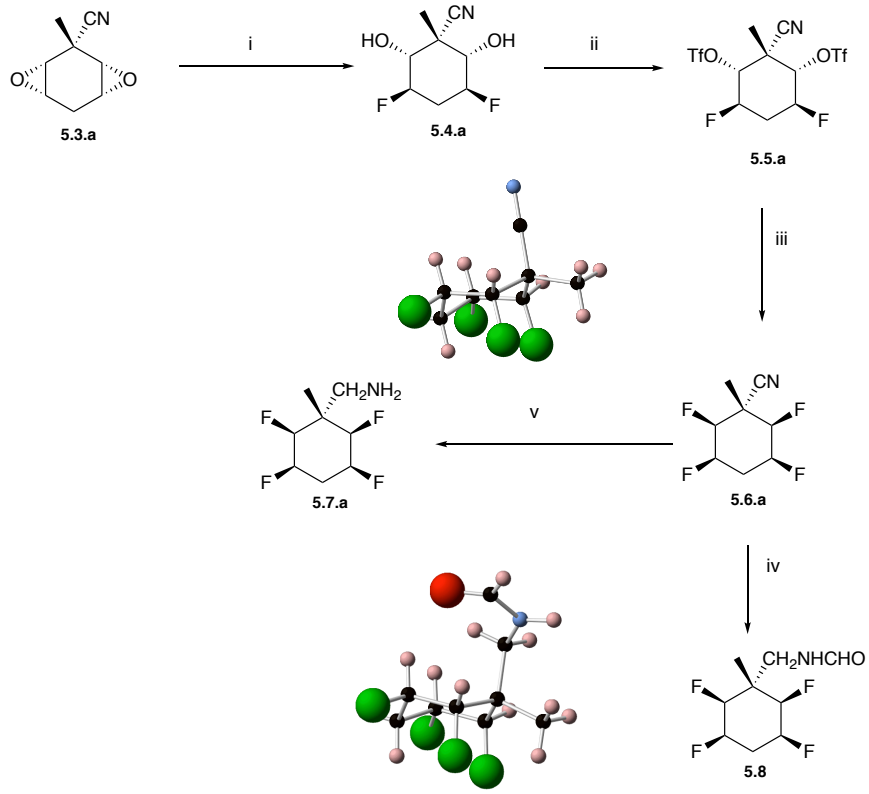
Entry	Conditions	Result		
1	*m*CPBA (4.9 eq.), DCM, 48 h, 35 °C	 **5.3.a**	 **5.3.b**	 **5.3.c**
		ratio **10**	**15**	**13**
2	*t*-BuOOH (1.2 eq.), VO(acac)r (0.025 eq.) dry benzene, 40 °C , 24 h		N/a	
3	2,2,2-Trifluoroacetophenone (0.05 eq.), 30% aqueous H_2O_2 (2 eq.), MeCN (2 eq.), *t*-BuOH, aqueous buffer solution (0.6 M K_2CO_3, 4 x 10^{-5}M EDTA tetrasodium salt), rt, 5 h, 35 °C, 18 h.		N/a	

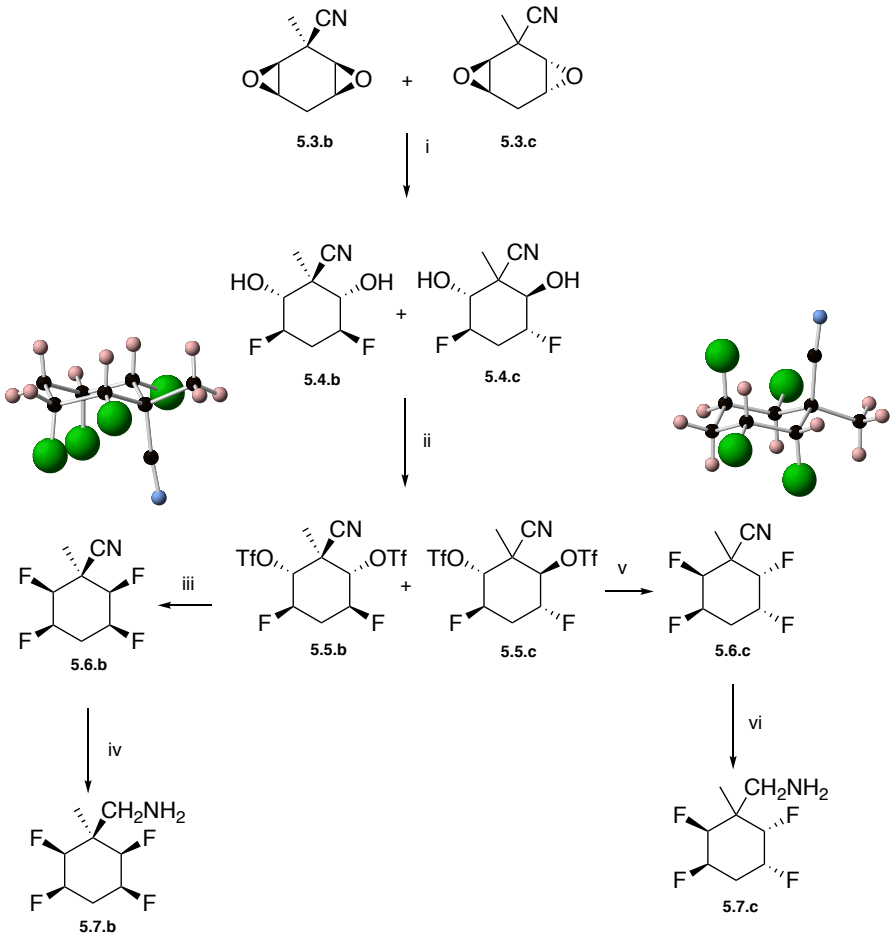
Table 5.1: Epoxidation reactions of cyclohexadiene 5.2; 1) *m*CPBA; 2) Vanadium-Catalyzed Epoxidation resulted in no conversion; 3) Epoxidation with 2,2,2-trifluoroacetophenone and H_2O_2 resulted in no conversion.

Tetrafluorocyclohexane nitrile **5.6.a** was found to be a crystalline solid, and its structure and stereochemistry was confirmed by X-ray crystallography, revealing the nitrile functional group to be on the opposite face to the fluorine atoms (Scheme 5.3).



Scheme 5.3: Reagents and conditions: (i) $Et_3N.3HF$ (8 eq.), 18 h, 140 °C; (ii) Tf_2O (4 eq.), pyridine, 1 h, 0 °C, 3 h, rt, 30%; (iii) $Et_3N.3HF$ (10 eq.), 4 days, 120 °C, 30%; (iv) 10% Pd/C (10 mol %), H_2, Et_3N/ HCOOH: molar ratio 1:37, THF, 18 h, RT; 78%; (v) $NaBH_4$ (10 eq.) / $NiCl_2.6H_2O$ (5 eq.), MeOH, 1 h, 0 °C, 18 h, rt, 50%;

The reaction was monitored by ^{19}F-NMR, and even though the conversion of **5.6.a** was shown to be almost quantitative, the isolated yield was modest. This was in part due to the fact that although the compound was crystalline, it was also found to be volatile and easily sublimed under reduced pressure. Hydrogenation (10% Pd/C in ethyl acetate) of **5.6.a** to form amine **5.7.a** proved difficult, as conversions were unreliable and low**.** [13–15] The structure and stereochemistry of **5.7.a** was confirmed by X-ray crystallography (Scheme 5.3). In order to improve this conversion, the hydrogenation reaction was repeated under similar conditions but with the addition of formic acid and triethylamine (molar ratio 37:1).[14] The result was the formation of an unanticipated formamide **5.8** but in very good yield (78%)(Scheme 5.3).[14] This compound was also found to be a crystalline solid and its structure was subsequently verified by X-ray crystallography (Scheme 5.3).



Scheme 5.4: Reagents and conditions: (i) $Et_3N.3HF$ (8 eq.), 18 h, 140 °C; (ii) Tf_2O (4 eq.), pyridine, 1 h, 0 °C, 3 h, rt, 40% (5.5.b), 15% (5.5.c); (iii) $Et_3N.3HF$ (10 eq.), 4 days, 120 °C, 51% (5.6.b), 31% (5.6.c); (iv) $NaBH_4$ (10 eq.)/ $NiCl_2.6H_2O$ (5 eq.), MeOH, 1 h, 0 °C, 18 h, rt, 65% (5.7.b), 23% (5.7.c).

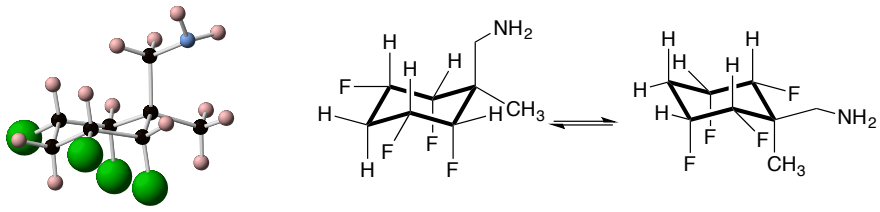
Treatment of nitrile **5.6.a** with nickel chloride and sodium borohydride, proved superior to direct hydrogenation, which lead to a full reduction of the nitrile to the amine (Scheme 5.3).[16,17]

A similar synthetic protocol was applied to the mixture of diastereoisomers of diepoxides **5.3.b** and **5.3.c**, which began with deoxyfluorination of the isomeric mixture ($Et_3N.3HF$, 140 °C). This gave an inseparable mixture of difluoro diols **5.4.b** and **5.4.c** (Scheme 5.4)**.** This mixture of isomers was then treated with triflic anhydride to furnish **5.5.b** and **5.5.c**. These isomers were readily separated by column chromatography. As such, the final fluorination of **5.5.b** and **5.5.c** was carried out on the separated isomers, but under similar conditions, resulting in the nitriles **5.6.b** and **5.6.c** respectively (Scheme 5.4).

The structures and stereochemistry of both **5.6.b** and **5.6.c** were also confirmed by X-ray structure analysis, as shown in Scheme 5.4. Each of these nitriles was individually reduced with nickel chloride/$NaBH_4$, furnishing tetrafluoro amine **5.7.b** and **5.7.c.** Tetrafluoro amine **5.7.b** was also found to be a crystalline solid and its structure was confirmed by X-ray analysis (Figure 5.2). The racemic amine **5.7.c**, was found to be a colourless liquid.

X-Ray analysis of the tetrafluoro amine diastereoisomers **5.7.a** and **5.7.b** revealed that in compound **5.7.b**, the more sterically demanding methyl amine occupies an equatorial position but in the crystal structure of compound **5.7.a**, the methyl amine sits in the axial position (Figure 5.1). Although this is the case in solid state it does not necessary extend to solution. Indeed it could be seen that both of the ^{1}H and ^{19}F NMR spectra of **5.7.a** and **5.7.b** have broad peaks. This can be attributed to fast interchange between the two chair conformations at room temperature.

5.7.a



5.7.b

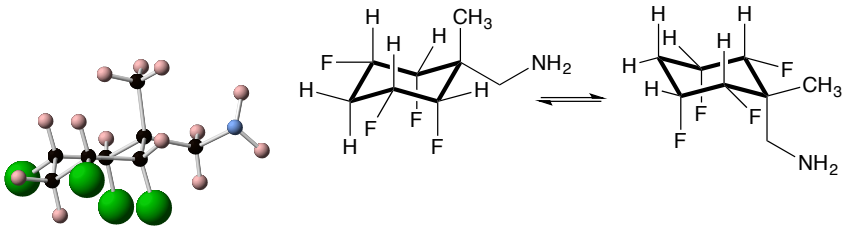
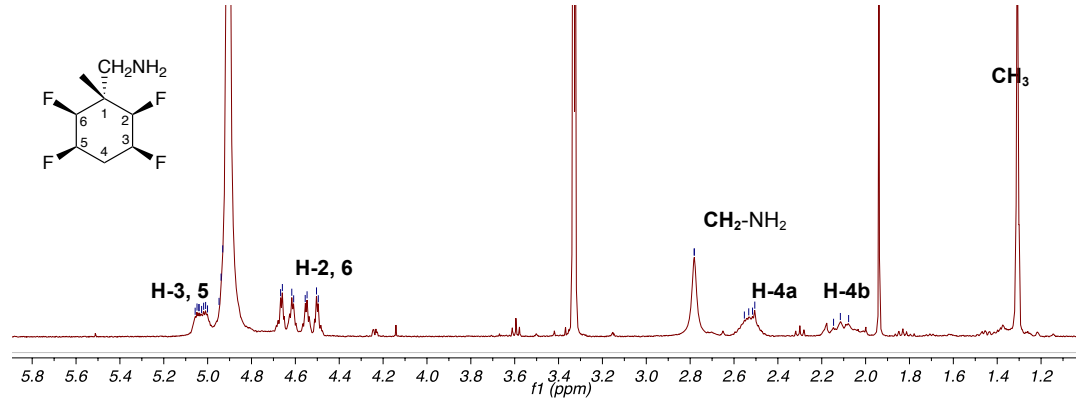


Figure 5.1: X-ray structures and chair conformations of compounds 5.7.a and 5.7.b

NOESY experiments of isomers **7.5.a** and **7.5.b** were conducted, separately irradiating the proton signals of the CH_3 group, the CH_2-N and H-$4_{a/b}$ hydrogen atoms (Figures 5.2 and 5.3, for full NOESY spectra see Supplementary, section 7.33). The NOESY spectra for compound **5.7.a** supported the conformer found by X-ray crystallography. Irradiating the CH_3 protons (at δ 1.40 ppm), perturbed signals at δ 4.61 ppm (corresponding to H-2, 6) and δ 2.9 ppm (corresponding to CH_2-N) consistent with the conformer summarised in Figure 5.2.

5.7.a: *^{1}H (400 MHz, MeOD)*



1D selective ^{1}H NOESY

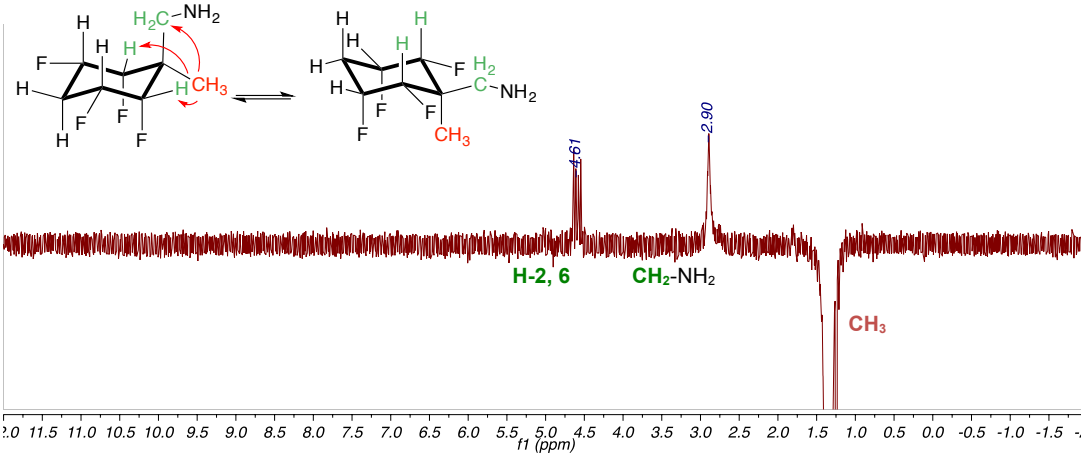
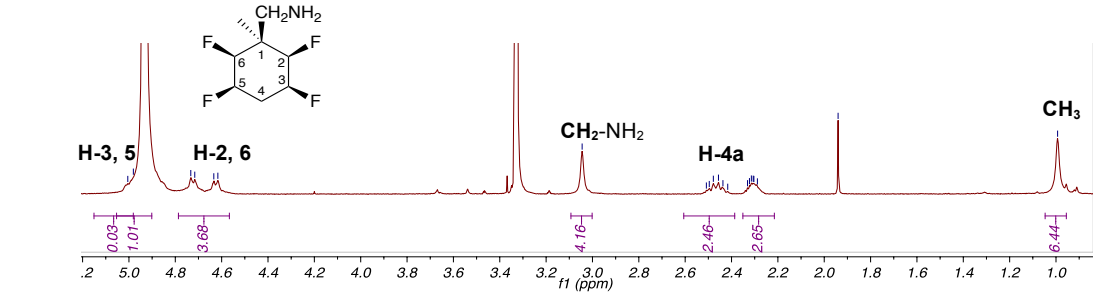


Figure 5.2: ^{1}H NMR Spectrum (top); 1D selective ^{1}H NOESY: Irradiation of CH_3 at rt (bottom) of compound 5.7.a

A similar set of experiments was conducted for diastereoisomer **5.7.b**. Irradiation of the CH_3 group perturbed the signal at δ 4.92 ppm (corresponding to protons H-3, 5), again consistent with the X-ray structure. No other signals were perturbed and thus no evidence of a second conformer (Figure 5.3). These NOESY experiment confirmed the dominance of the X-ray conformers in solution.

5.7.b: *^{1}H (400 MHz, MeOD)*



1D selective ^{1}H NOESY

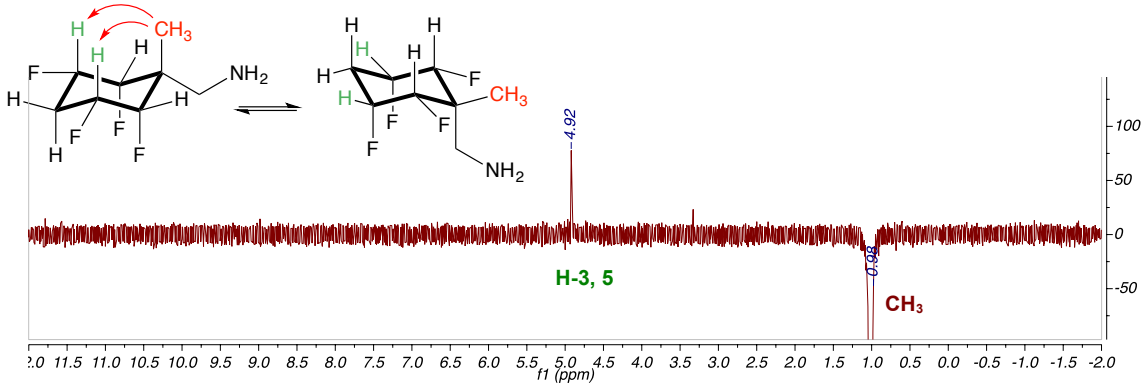


Figure 5.3: ^{1}H NMR Spectrum (top); 1D selective ^{1}H NOESY: Irradiation of CH_3 at rt (bottom) of compound 5.7.b

It was decided to explore VT NMR experiments for compound **5.7.b.** The resultant ^{19}F NMR spectrum recorded at -40 °C is in Figure 5.4. There is a minor conformer present in a 7:1 ratio (Figure 5.4).

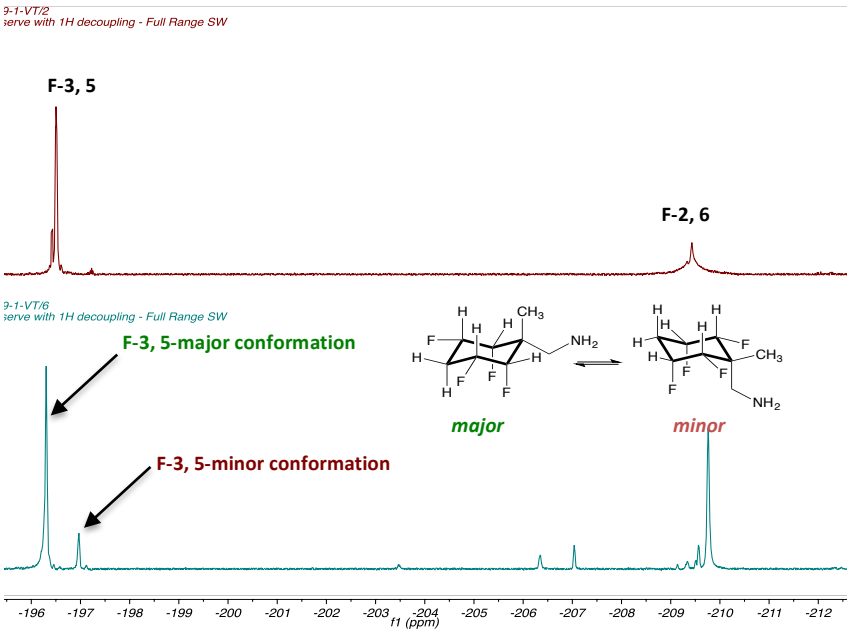


Figure 5.4: VT experiment for compound 5.7.b; ^{19}F NMR with ^{1}H decoupling at rt (top); ^{19}F NMR with ^{1}H decoupling at -40 °C (bottom);

5.3. Incorporation of the all-*cis*-2,3,5,6-tetrafluorocyclohexylamine motifs into *bis*-systems.

Since the majority of tetrafluoro cyclohexane motifs have been found to be crystalline, it was an attractive prospect to study the intermolecular interactions and supramolecular arrangements, which might be dictated by the electrostatic ordering of the cyclohexane rings. X-ray structure analysis should reveal modes of ring stackings. It was also of interest to demonstrate that motif **5.7** is reactive enough to allow its introduction into more complex molecular architectures, and then explore its supramolecular arrangements.

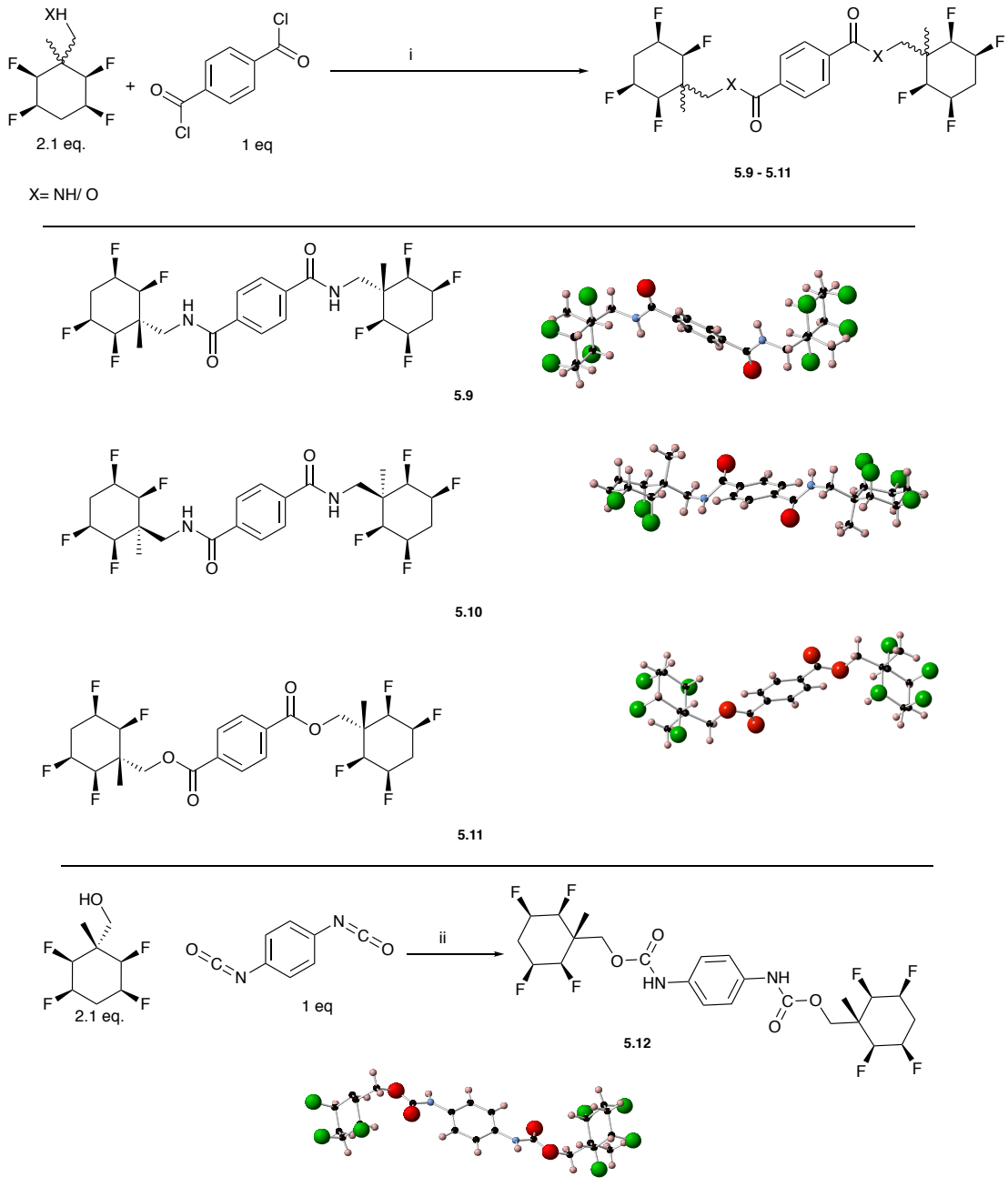
Supramolecular chemistry can be define as ''the chemistry of the noncovalent bond'' where noncovalent interactions account for molecular stability in complexes across nanoscience, including studies in biochemistry and materials.[18,19] Crystal packing analysis proved to be an invaluable tool in the exploration of the forces acting within the solid state of metallic, covalent, ionic, and molecular crystals.[20] In relation to this research the main interest will focus on molecular crystals, where the supramolecular arrangement is dictated by cyclohexane ring stacking. Non-covalent interaction can be classified into two main groups- 'mostly physical forces' and 'mostly chemical forces'.[20] While physical forces include van der Waals non-bonded interaction such as dispersion/ London and repulsive forces, hydrophobic and electrostatic interactions, chemical forces contain hydrogen bonding interactions and charge transfer (CT) interactions, which also include halogen bonding.[20]

Due to high molecular dipole of the facially polarized tetrafluoro cyclohexane motifs, it is of interest as to whether certain conformations arise due to the specific electrostatic interactions exhibited by these organofluorine motifs and can then dictate the supramolecular arrangement.

For this purpose the generation of *bis*-systems was envisaged, whereby terephthaloyl bridges would connect two tetrafluoro cyclohexane motifs.

Consequently one objective of this project was to explore the molecular self-assembly of higher order fluorinated *bis*-amide systems in the solid state, using both tetrafluoro cyclohexane amine derivatives **5.7.a** and **5.7.b** as the amine components. A comparative ester, rather then an amide was also prepared to compare systems with and without the amide linker, because intermolecular hydrogen bonding between the amides may dominate the packing. The general esterification procedure used to obtain these *bis*-systems was performed with terephthaloyl chloride in presence of amines **5.7.a**, **5.7.b** or alcohol **3.9.a** (2.1 eq.).

As a result, *bis*-systems **5.9**, **5.10** and the ester **5.11** were obtained in reasonable yields (79%, 48%, and 88%) (Scheme 5.5).[21,22] A similar reaction was performed with 1,4-phenylene diisocyanate in the presence a catalytic amount of triethylamine in toluene and **3.9.a**, to furnish **5.12** in 91% yield (Scheme 5.5). [23,24]



Scheme 5.5: Synthesis of 5.9-5.11: (i) Terephthaloyl chloride (1 eq.), Et_3N (4 eq.), DMAP (20 mol %), DCM, 18 h, rt, 79% (5.9), 48% (5.10), 88% (5.11) ; Synthesis of 5.12: (ii) Et_3N (0.1 eq.), Toluene, 4 h, 60 °C (91 %).

The *bis*-compounds **5.9-5.12** were all found to be solids that possessed low solubility in a wide range of solvents and a suitable crystal of each was obtained and subjected to X-ray analysis. The intermolecular packing **5.9**, **5.10**, **5.11** and **5.12** was analyzed after X-ray crystallography (Scheme 5.4 and Figure 5.5).

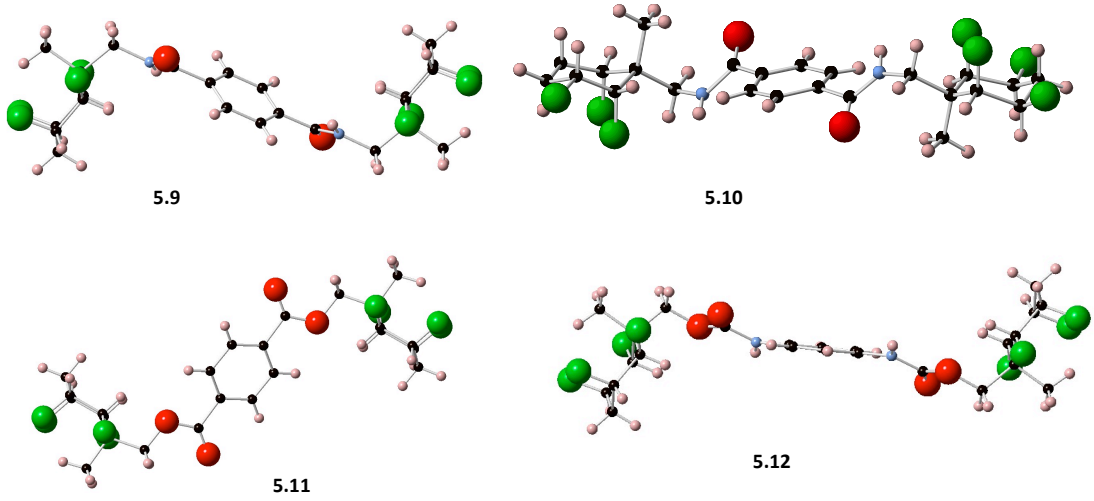


Figure 5.5: X-ray structures of compounds 5.9-5.12.

It was immediately clear that the negative fluorous faces and positive protic faces of the tetrafluorocyclohexane rings were orientated relative to each other in all cases (Figure 5.5). The general trend for these compound*s* is a columnar stacking pattern, where neighboring molecules stuck on top of each other rather.

The less sterically demanding methyl groups relative to the methylene moiety of the cyclohexane moieties all occupy axial positions (Figure 5.6). X-Ray crystallography revealed that for **5.9, 5.11** and **5.12**, the methyl is *syn* to the four fluorine atoms of the ring and is positioned among them occupying an axial orientation. By contrast for compound **5.10**, the methyl group is sited on the opposing face to the fluorine atoms in the cyclohexane ring and positions itself between the fluorine faces of two neighboring molecules, without affecting the electrostatic stacking of the facially polarised rings (Figure 5.6).

For compounds **5.9** and **5.10** with carboxamide linker, a significant contribution to the stacking structure appears to come from intermolecular hydrogen bonding between the amide groups, with N-H---O=C distances of 2.04 Å, 2.45 Å (Figure 5.6). Carbamate **5.12**, also had a distance between neighboring N-H---O=C of 2.9 Å, indicating a weak hydrogen bonding.

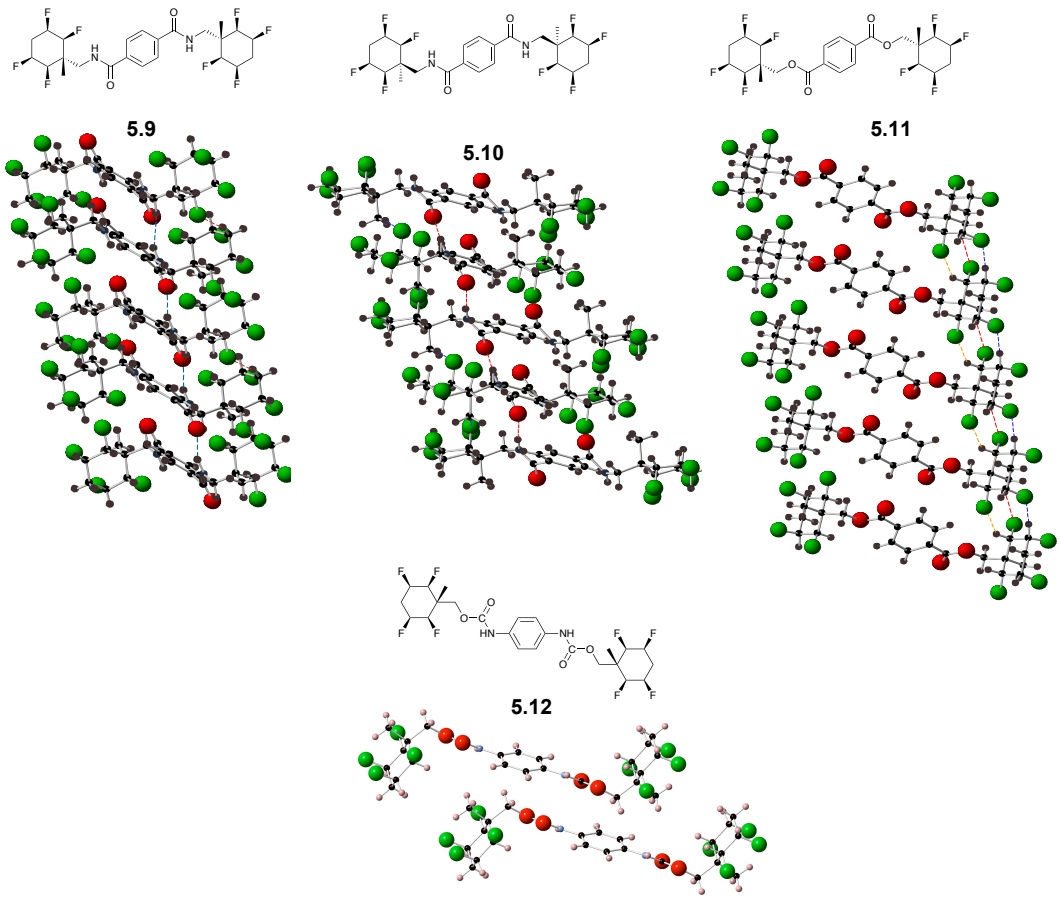


Figure 5.6: X-ray structures and crystal packing of compounds 5.9, 5.10, 5.11, 5.12.

Even though intermolecular hydrogen bonding between N-H and O=C is observed within those systems and found to bring neighboring molecules together, this is not the defining aspect of the columnar packing pattern. A control comparison was made with ester **5.11** showing that even when there are no hydrogen bonds to link structures, the columnar stacking pattern was still observed. Electrostatic attractions between the cyclohexyl rings appears to be significant. The closest intermolecular distances between fluorine of one cyclohexane ring and the hydrogen atoms on the cyclohexane ring of the nearby molecule were found to be 2.45 Å (**5.9**), 2.49 Å (**5.10**), 2.50 Å (**5.11**), 2.35 Å (**5.12**) (Figure 5.6). These are too long to indicate F-H hydrogen bonding and suggest that the packing pattern is largely governed by physical electrostatic forces of negative fluorine faces and positive hydrogen faces of neighboring rings.

5.5. Conclusion.

This study has demonstrated a method for the preparation of a new type of 2,3,5,6-tetrafluorocyclohexane amine motifs. Through a five-step synthesis, where diepoxidation furnished the three diastereoisomers **5.3.a**, **5.3.b** and **5.3.c**, the corresponding diastereoisomers of the fluorinated nitrile derivatives (**5.7.a**, **5.7.b** and **5.7.c**) were obtained. Reduction of the 2,3,5,6-tetrafluorocyclohexane nitrile derivatives furnished three tetrafluoro amine isomers, which represent novel building blocks with the potential to be widely used including applications in drug discovery. The reactivity of these building blocks was demonstrated through a set of condensation reactions, whereby amine derivatives **5.7.a**, **5.7.b** along with the alcohol **3.9.a** were used to prepare *bis*-compounds **5.9**-**5.12**.

Each of these *bis*-compounds was then studied using X-ray crystallography to reveal the architecture of their molecular self-assembly. Firstly the supramolecular arrangement of the *bis*-compounds was found to have highly structured columnar stacking pattern rather than an interdigitated assembly, with the fluorinated faces of the cyclohexane moiety containing the protic faces of the adjacent molecules. The supramolecular arrangements of these systems is composed of a range of non-covalent interactions, including hydrogen bonding, repulsive and electrostatic forces. However, in comparison studies of *bis*-systems with carboximide and carbamate bonds (**5.9**, **5.10** and **5.12**) that participate in hydrogen bonding and ester *bis*-systems without such interactions (**5.11)** the columnar stacking pattern is retained, suggesting that the facially polarized fluorinated cyclohexane rings can dictate the supramolecular arrangement.

5.6. References.

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Chapter 6. Conclusion and Future Work.

6.1. Conclusion.

Through the course of these chapters, which describe the development of novel all-*cis*-tetrafluoro motifs, a chemical library of a range of building blocks has been obtained including alcohols, carboxylic acids, amines and amino acids (Figure 6.1).[1–3] The methods of their synthesis has proved reliable and reproducible on demand. Some of the building blocks have already been used in creating peptidomimectics through 4-UCC reactions and peptide couplings (Chapters 2 and 3), as well as α-fluoroamides to explore intermolecular and intramolecular interactions (Chapters 3 and 5).

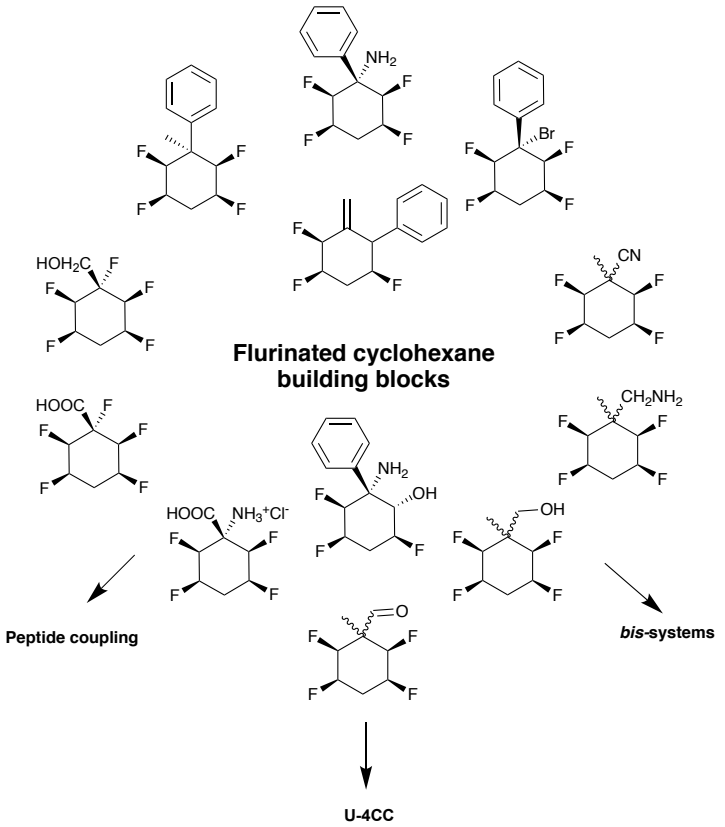


Figure 6.1: Fluorinated cyclohexane building blocks.

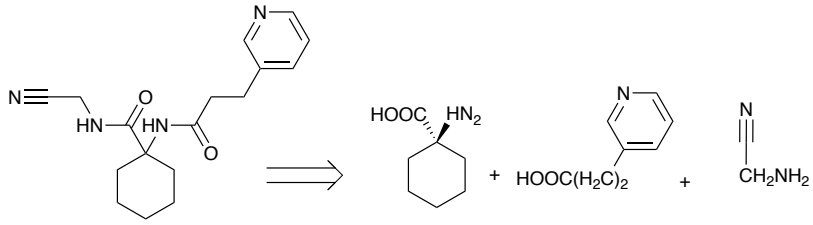
6.2. Future Work.

6.2.1. Finding bioactive candidates with structural similarities.

With such a variety of building blocks in hand it will be possible now to search for bioactive drug-like candidates, where those novel fluorinated motifs can be incorporated.

Chapter 1 explained how introduction of fluorine into a drug candidate could produce positive outcomes on metabolic stability, pharmacokinetic properties, conformation, pK_a and lipophilicity. The following section will describe a few ideas where fluorinated cyclohexanes may be applied.

One of the first criteria for such candidates was the structural similarity, such as a cyclohexane ring. Some bioactive molecules contain a cyclohexane ring, where its presence serves some function in the bioactivity.



6.1

Figure 6.2: Peptidomimetic nitrile first generation lead compound

Compound **6.1**, has been the lead compound in the development of Falcipain-2 inhibitors against the malarial parasite *Plasmodium falciparum* (Figure 6.2).[4] The cyclohexane ring is a key structural aspect of this inhibition, hence installation of the fluorinated cyclohexane such as amino acid **2.7** (prepared in Chapter 2), offers an interesting option for the development of new Falcipain-2 inhibitors.

Another example where introduction of the all-*cis*-fluorinated cyclohexane moiety could be beneficial is in trisubstituted benzimidazoles, new group of drugs being developed against Tuberculosis (TBa).[6] One of the main structural features of the first generation lead compounds is the cyclohexyl ring (R^1, Figure 6.3), which was found to play a critical role in the antituberculosis activity. Optimization of the second generation demonstrated that addition of fluorine on the phenyl ring (R^2, Figure 6.3) enhanced antibacterial activity, and also improved metabolic and plasma stability.[7] Both moieties, R^1 and R^2, are good candidates for substitution by fluorinated motifs, such as pentafluoro carboxylic acid **2.11** (Chapter 2), which is reactive towards peptide coupling (Figure 6.3).

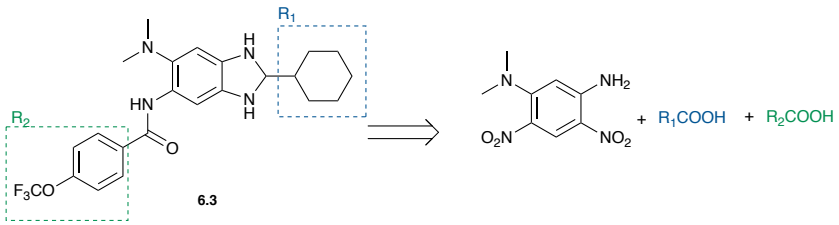


Figure 6.3: Trisubstituted Benzimidazole derivative, FtsZ protein inhibitor (6.3)

The scope of potential candidates where the novel building blocks can be installed is very diverse, however some preferences and limitations should be considered.[4-8] Firstly, to avoid the elimination of fluorine on the cyclohexane ring, synthetic steps towards target compound should exclude the use of strong bases and installation of the fluorinated building block is most preferable towards the end of the synthetic route. The bioactive candidate should contain structurally similar moiety to the cyclohexane ring. Fluorinated substituents could be particularly effective if the mode of inhibition operates through blocking the metabolism of the targeted enzyme.

6.2.2. Finding the binding interactions.

It will be important to understand how this motif interacts with proteins. A useful way for finding a good biological candidate that the tetrafluoro cyclohexane motif can interact with, is through protein 'pull down assays'. This technique has been used as an initial screen to identify novel protein-small molecule interactions. With a range of novel fluorinated motifs, it will be useful to know what interactions can be formed to proteins.

The three main stages in this procedure, shown in Figure 6.4, involve firstly labelling the fluorinated building block with a tag, such as biotin. Addition of the cell lysate from the organism of interest allows the proteins to bind fluorinated moiety. The biotinated fragment with bound proteins is then removed by adsorption to biotin-containing resin and the remaining proteins are eluted away. Finally the bound proteins are eluted off the resin with high salt buffer for proteomic analysis.[9]

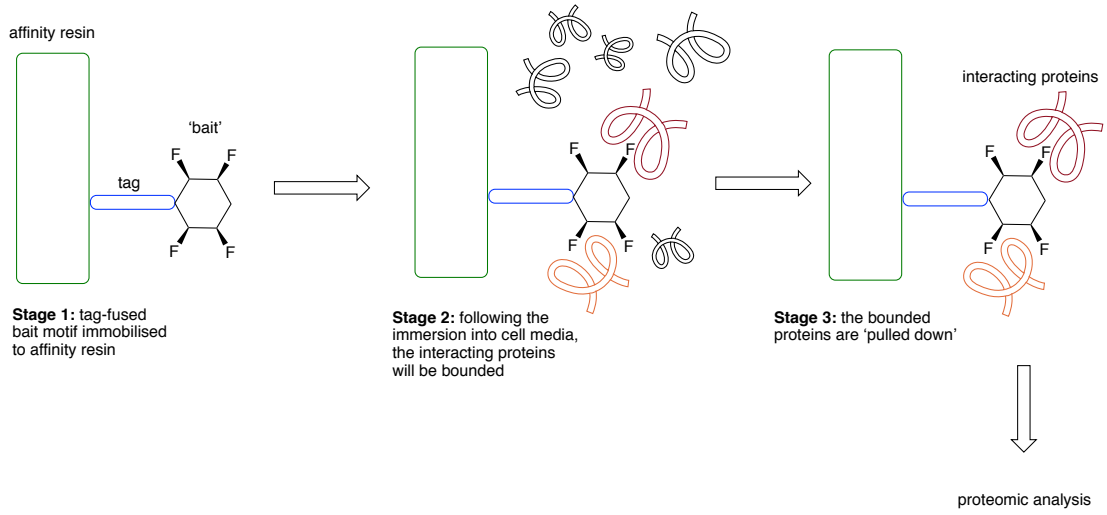


Figure 6.4: General process for protein 'pull down assays'.

6.2.3. Exploring the physiochemical properties if the all-*cis*-tetrafluorocyclohexane rings.

Beside the bioactivity studies, the increased hydrophobicity of these novel building blocks could also be beneficial.[10, 11] The St Andrews group have recently shown a significant increase in hydrophilicity with increasing fluorination on the cyclohexyl ring system, showing at least a 100 fold decrease in log P than their non-fluorinated cyclohexane counterparts.[11]

These physiochemical features in addition to the unique facial polarity of tetrafluoro cyclohexane motifs make it an attractive prospect for inclusion in drug development or agrochemical studies.

6.3. References.

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Chapter 7. Experimental.

7.1. General information.

Air and moisture sensitive reactions were carried out under an argon atmosphere in flame-dried glassware. Room temperature refers to 18-25 °C. All evaporations and concentrations were performed under reduced pressure (*in vacuo*).

Thin Layer Chromatography

Thin layer chromatography was carried out on aluminium-backed Merck TLC silica gel 60 F_{254} plates. TLC plates were observed under UV light (254 nm and 266 nm) before being stained by alkaline potassium permanganate or ninhydrin solutions and developed by heating.

Flash Silica Gel Column Chromatography

Column chromatography was performed on Merck Geduran silica gel 60 (250-400 mesh) under a positive pressure of compressed air eluting with solvents (reported as *v/v*) as supplied. Reverse phase column chromatography was performed using Extract Clean C18-HC prepacked cartridges.

Purification by HPLC

HPLC semi-preparations were performed using either or a Shimadzu Prominence system (SIL-20A HT autosampler, CL-20AT ternary pump, DGU-20A3R solvent degasser, SPD 20A UV detector and CBM-20A controller module) with reverse phase column (Phenomenex Luna C18 (250 × 10.00 mm, 5µ). All solvents used were HPLC grade and were degassed prior to use by bubbling nitrogen through the solvents.

Samples were freeze dried from frozen solutions in H_2O in a Christ Alpha 1-2 LO Plus freeze drier.

Chemicals

All chemicals were purchased from Acros, Sigma Aldrich, Alfa Aesar, Fisher Scientific, Fluorochem, TCI UK, Apollo, or Merck. Anhydrous solvents (Et_2O, THF, CH_2Cl_2, Toluene) were obtained from MBraun MB SPS-800 solvent purification system by passage through two drying columns and dispensed under an argon atmosphere. Triethylamine and pyridine were distilled from KOH and stored over KOH. Brine refers to sat. aq. sodium chloride solution.

Petroleum ether refers to the fraction with a boiling point between 40-60 °C. All chemicals were used as supplied, expect when necessary, chemicals were purified as described.

NMR

All NMR spectra were recorded using a Bruker Avance III 500, Bruker Avance II 400, Bruker Avance 300 or 500 spectrometers. The deuterated solvent was used for an internal deuterium lock. ^{1}H NMR spectra were recorded at either 300, 400 or 500 MHz. . ^{13}C NMR chemical shifts were reported to one decimal place. ^{13}C NMR spectra were recorded using the DEPTQ pulse sequence and broadband proton decoupling at either 75, 100 or 126 MHz. ^{19}F NMR chemical shifts were reported to one decimal place and spectra were recorded at 282, 376 or 470 MHz. All chemical shifts, δ, are stated in units of parts per million (ppm), relative to a standard, for ^{1}H NMR and ^{13}C NMR the reference point is TMS δ_H and δ_C 0.00 ppm. For ^{19}F NMR the reference point is CCl_3F δ_F is 0.00 ppm. ^{1}H NMR chemical shifts were reported to two decimal places. All spectra are referenced to the residual solvent signal of the deuterated solvent. Data processing was carried out using MestReNova 9.0.1. Chemical shifts are reported in parts per million (ppm) and coupling constants (*J*) are reported in Hertz (Hz). The abbreviations for the multiplicity of the proton, carbon and fluorine signals are as follows: s singlet, d doublet, doublet of doublets, ddd doublet of doublet of doublets, dddd doublet of doublet of doublet of doublets, dt doublet of triplets, q quartet, m multiplet, br s broad singlet. When necessary, resonances were assigned using two-dimensional experiments (COSY, HSQC, HMBC, TOCSY).

1D selective ^{1}H, ^{19}F-HOESY NMR was carried out by Dr Tomas Lebl and James Montgmery on a Bruker Avance 500 spectrometer.

Dynamic NMR analysis was carried out by Dr Tomas Lebl. ^{19}F NMR were recorded at multiple temperatures in CD_2Cl_2 on a Bruker Avance 500 spectrometer. The temperatures were accurately determined using a 4% CH_3OH in CD_3OD solution. Complete lineshape analysis was carried out using the Bruker Topspin D-NMR module.

Melting Points

Melting points were determined using a Griffin MPA350 or a Electrothermal 9100 melting point apparatus and are uncorrected.

Mass Spectrometry

High and low resolution mass spectra were obtained by electron impact (EI), electrospray (ES), chemical ionisation (CI), atomospheric pressure chemical ionisation (APCI). These spectra were obtained by Caroline Horsburgh (University of St Andrews) and the EPSRC National Mass Spectrometry Service Centre, Swansea. The electrospray samples were obtained using a Micromass LCT spectrometer. Chemical ionisation and electron impact was obtained using a Micromass GCT spectrometer. Atomospheric pressure chemical ionisation samples were obtained using an LTQ Orbitrap XL spectrometer. Electron impact samples were obtained using a Micromass GCT spectrometer or a Finnigan MAT 95 XP. *m/z* values are measured in Daltons.

IR

Infrared spectra were acquired on a Perkin Elmer Spectrum GX FTIR apparatus spectrometer either as KBr pellets, or as a thin film between NaCl plates, or on a Shimadzu IRAffinity-1S spectrometer with a diamond ATR attachment. Absorption maxima are reported in units of wavenumbers (cm-1). Melting points were recorded on an Electrothermal IA9100 melting point apparatus, or on a Griffin MPA 350.BM2.5 melting point apparatus and are uncorrected.

Single Crystal X-Ray Analysis

Single Crystal X-Ray Analysis was carried out by Prof. Alexandra Slawin, using either a molybdenum or copper X-ray source. The molybdenum system used a MM-007 high-brilliance generator with VariMax optics and either an AFC8/Saturn 70 or an AFC7/Mercury detector. The copper system used a MM-007 high-brilliance generator with an AFC10/Saturn 92 detector. The .cif files for the X-ray structures obtained are included on the attached CD.

DFT Computations

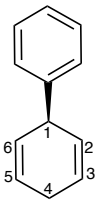
A conformational analysis was performed by Prof. Michael Buehl for a model amide at the B3LYP[vi]/6-311+G** level of density functional theory.

7.2. Procedures and analytical data

7.2.1. Chapter 2.

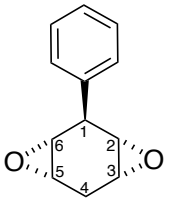
The route towards 1.112 was followed by the reported literature synthesis, where ^{1}H NMR of synthesized compounds 1.05-1.112 have been compared and found to be consistent with previously reported data.[1,2]

Cyclohexa-2,5-dien-1-yl benzene (1.115)[3]



A solution of biphenyl **1.114** (22.95 g, 150 mmol, eq 1.0) in diethyl ether (500 mL) was added to liquid ammonia (400 mL) at –78 °C. Lithium (2.3 g, 110 mmol, eq 2.2) was added portionwise to the reaction over 10 min, resulting in the formation of deep blue-brown colour. The reaction was warmed to –25 °C and stirred for 30 min. The reaction was then quenched with the addition of solid ammonium chloride (120 g), resulting in a colourless suspension. This mixture was then warmed to RT and water (300 mL) was added slowly, followed by diethyl ether (200 mL). The organic layer was separated and washed with water (2 x 200 mL). The aqueous layers were extracted with diethyl ether (200 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield 3-phenyl-1, 4-cyclohexadiene **1.115** as a colourless oil (22.8 g, quant.). No further purification was required; ^{1}H NMR has been compared and consistent with previously reported synthesis; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.37 (2H, m, Ar), 7.33-7.23 (3H, m, Ar), 5.92-5.87 (2H, m, CH-3, 5), 5.83 -5.76 (2H, m, CH-2, 6), 4.05-3.40 (1H, m, H-1), 2.88-2.73 (2H, m, H-4);

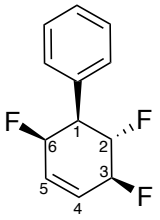
(1RS,2SR,3SR,5RS,7SR)-2-Phenyl-4,8-dioxatricyclo[5.1.0.0^{3,5}}]octane (1.116)[3]



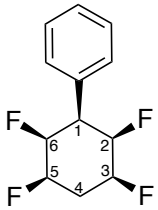
*m*CPBA (17 g, 70%, 65 mmol, eq 2.1) was added at 0 °C to a solution of 3-phenyl-1,4-cyclohexadiene **1.115** (5.0 g, 32 mmol, eq 1.0) in DCM (250 mL). The reaction was slowly warmed to RT and stirred for 14 h. The reaction was washed with aq. KOH (10 %, 250 mL). The aqueous layer was then extracted with DCM (3 x 250 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to give a colourless crystalline solid. This was purified by silica gel column chromatography (eluent: EtOAc/hexane = 1/4) to yield pure **1.116** (4.9 g, 27 mmol, 83%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.31 (5H, m, Ar), 3.96-3.98 (1H, m, H-1), 3.21-3.18 (2H, m, H-3, 5), 3.11-3.08 (2H, m, H-

2, 6), 2.94-2.92 (1H, m, H-4a), 2.43 (1H, dt, J=17.1, 2.8 Hz, H-4b).

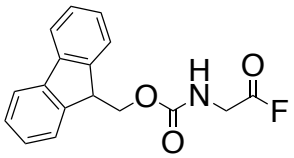
(3RS,4SR,5SR,6SR)-3,4,6-trifluoro-5-phenylcyclohexene (1.121) and (1RS,2SR,3RS,4RS,5SR)-1,2,4,5-tetrafluoro-3-phenylcyclohexane (1.122)[3]



$Et_3N{\cdot}3HF$ (28.5 mL, 174 mmol, eq 8.0) was added to a solution of Phenyl-dioxatricyclo-octane (4.1 g, 22 mmol, eq 1.0) at RT in dried THF (6 mL). After stirring at 130 °C under argon atmosphere for 40 h, the mixture was cooled to RT and was poured into sat. aq. Sodium bicarbonate (500 mL) at 0 °C. The mixture was extracted into DCM (4 x 200 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The mixture of difluorohydrins **1.117** and **1.118** was dissolved in dried DCM (150 mL) under an argon atmosphere. To the solution was added pyridine (6.4 mL, 80 mmol, eq 4.0) and trifluoromethanesulfonic anhydride (310 mL, 60 mmol, eq 3.0) at -40 °C and the mixture was allowed to warm to RT. After stirring for 21 h, the mixture was filtered through a small pad of silica gel (eluent: petroleum ether/DCM/EtOAc = 1/1/1) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether/DCM/diethyl ether = 8/4/1) to give a mixture of ditriflates **1.119** and **1.120** (8.1 g, 16.5 mmol, 75%, 9:10 = ca. 1.6:1) as a colourless powder. To a solution of this mixture of ditriflates **1.119** and **1.120** in dried THF (5 mL) was added $Et_3N{\cdot}3HF$ (21.0 mL, 130 mmol, eq 8) at RT. After stirring at 100 °C under argon atmosphere for 60 h, the mixture was cooled to RT and was poured into sat. aq. sodium bicarbonate (600 mL) at 0 °C. The mixture was extracted with DCM (4 x 200 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The trifluoro-phenylcyclohexene **1.121** (979 mg, 4.62 mmol, 28%) and 2,3,5,6-tetrafluoro-phenylcyclohexane **1.122** (1.15 g, 4.95 mmol, 30%) as colourless crystalline solids; **1.121**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.31 (5H, m, Ar), 6.17-6.03 (2H, m, H-4,5), 5.48-5.14 (2H, m, H-2, 3), 4.98-5.01 (1H, m, H-6), 3.17 (1H, m, H-1); ^{19}F NMR (376 MHz, $CDCl_3$) δ -176.5 (d, *J* 10.5 Hz, F-6), -185.6 (dd, *J* = 14.3, 10.5 Hz, F-2), -195.3 (d, *J* = 14.3 Hz, F-3); followed by **1.122**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.48 (2H, m, Ar), 7.45-7.35 (3H, m, Ar), 5.18-4.94 (2H, m, H-2, 6), 4.76-4.53 (2H, m, H-3, 5), 2.88-2.76 (1H, m, H-4a), 2.63 (1H, t, *J* = 37 Hz, H-)1, 2.51 (1H, dt, *J* = 10.1, 5.1, Hz, H-4b); ^{19}F NMR (376 MHz, $CDCl_3$) δ -190.6 - (-190.7) (m, F-3, 5), -209.7-(-209.9) (m, F-2, 6).

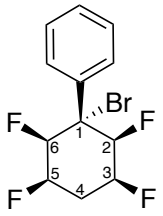


Preparation of Fmoc-Glycine fluoride with DAST



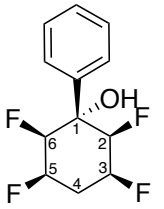
DAST (40 mg, 0.24 mmol) was added to a stirred solution of Fmoc-Glycine (60 mg, 0.2 mmol) in 10 ml of dry dichloromethane (DCM) at room temperature. After 10 min the mixture was extracted with ice water. The organic layer was separated and dried over $MgSO_4$. The solvent was removed under vacuum at room temperature. Recrystallization or precipitation from DCM/n-hexane gave Fmoc Glycine fluoride (0.44 mg, 0.15 mmol, 75%); M.p of obtained compound agree with the data from the literature.[4,5] M.p.= 140 °C (Literature M.P.= 140-141°C)[5]; ^{1}H NMR (376 MHz, $CDCl_3$): δ 7.80 (2H, dt, *J* = 7.6, 1.0, Ar), 7.61 (2H, d, *J* = 7.4, Ar), 7.49- 7.40 (2H, m, Ar), 7.35 (2H, td, *J* = 7.4, 1.2, Ar), 5.27 (1H, s, NH), 4.50 (2H, d, *J* = 6.9, CH_2-O), 4.27 (1 H, t, *J* 6.9, CH), 4.21 (2H, AA'XX', CH_2-COF); ^{19}F NMR (376 MHz, $CDCl_3$): δ +32.2.

((2*R*,3*R*,5*S*,6*S*)-1-bromo-2,3,5,6-tetrafluorocyclohexyl)benzene (2.1)



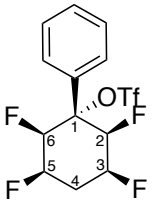
N-Bromosuccinimide (2.05 g, 113.79 mmol) was added to a solution of **1.122** (2.20 g, 94.82 mmol) in CCl_4 (20 ml) and the mixture was refluxed for 18 h. After the mixture was cooled to r.t, the solvent was removed under reduced pressure, dissolved in DCM and washed with H_2O and the aqueous layer was then extracted with DCM (200 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give orange solid, which was subjected to column chromatography using silica gel (petrol ether/DCM 7:3), furnishing compound **2.1** (2.62 g, 84.39 mmol, 89%): M.p.= 178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (2H, d, *J* = 7.2, Ar), 7.54-7.36 (3H, m, Ar), 5.70 (2H, dd, *J* = 48.4, 5.5, H-2, 6), 5.60-5.36 (2H, m, H-3, 5), 2.80-2.62 (1H, m, H-4a), 2.60-2.46 (1H, m, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.6 (Ar) , 129.6 (Ar) , 129.2 (Ar) , 126.4 (Ar) , 88.0 (dd, *J* = 199.0, 18.9, C-3, 5), 85.4 (dm, *J* = 201.5, C-2, 6), 56.8 (C-1) , 27.1 (tt, *J*= 22.3, 3.3, C-4); ^{19}F NMR (376 MHz, $CDCl_3$): δ -189.3 (AA'XX', F-2, 6), -194.7 (AA'XX', F-3, 5); IR: ν_{max}/cm^{-1} 2922.16 (C-H), 1392.61 (C-F), 1101.35 (C-F); FTMS (ESI$^-$) *m/z* calcd for ([M]) 311.1133; found 311.1116 (Δ 5.5 ppm).

(2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-phenylcyclohexanol (2.3)



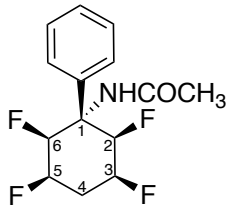
Benzyl bromide **2.1** (300 mg, 0.97 mmol) has been dissolved in DMF (10 mL) with sodium azide (100 mg, 1.54 mmol). The reaction mixture was stirred for 18 h at 90 °C until TLC analyses revealed the consumption of the starting material. The mixture was poured into water (50 mL), extracted with diethyl ether (2 × 100 mL), washed with brine (3 × 150 mL), dried over Na_2SO_4, filtered, and the filtrate was concentrated in a rotary evaporator under reduced pressure. Crude product has been purified by column chromatography using silica gel (petrol ether/ethyl acetate 7:3), furnishing compound **2.3** (2.62 g, 84.39 mmol, 82%): M.p.= 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.69 (2H, m, Ar), 7.59-7.38 (3H, m, Ar), 5.29-4.94 (4H, m, H-2, 3, 5, 6), 2.78-2.62 (1H, m, H-4a), 7.80-7.69 (1H, m, H-4b), 2.07 (1H, s, OH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.5 (Ar), 129.6 (Ar), 129.3 (Ar), 126.1 (Ar), 89.6 (dd, *J* = 196.8, 15.2, C-2, 6), 86.1 (dm, *J* = 191.1, C-3, 5), 73.1 (C-1), 26.7 (t, *J* = 21.9, C-4); ^{19}F NMR (376 MHz, $CDCl_3$): δ -198.8 (AA'XX', F-2, 6), -207.7 (AA'XX', F-3, 5); IR: ν_{max}/cm^{-1} 3578.01 (O-H), 2925.1 (C-H), 2853.73 (C-H), 1390.7 (-C-H), 1160.2 (C-F), 1013.61 (C-F); FTMS (ESI$^-$) *m/z* calcd for ([M]-H$^+$) 247.0746; found 247.0751 (Δ 2.1 ppm).;

(2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-phenylcyclohexyl trifluoromethanesulfonate (2.12)



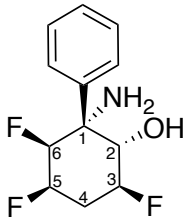
Trifluoromethanesulfonic anhydride (130 mg, 0.46 mmol) was slowly added to **2.3** (60 mg, 0.25 mmol) in pyridine (5 mL) at 0 °C. After 18 h stirring at rt, the reaction mixture was quenched with a mixture of water (50 mL) and $CuSO_4$ (2 mL) and extracted with diethyl ether (50 mL x 3). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by means of column chromatography (petroleum ether/DCM 7:3) to offer **2.12** (50 mg, 0.132 mmol, 54%) as white crystalline solid; M.P: 123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77-7.70 (2H, m, Ar), 7.68-7.56 (3H, m, Ar), 5.66 (2H, dd, *J* = 48.0, 6.9, H-2), 5.39 (1H, dd, *J* = 47.8, 6.5, H-6), 5.25-5.04 (1H, m, H-3, 5), 2.85-2.67 (1H, m, H-4a), 2.65-2.53 (1 H, m, H-4b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8 (Ar), 131.8 (Ar), 130.0 (Ar), 128.6 (Ar), 122.8 (q, *J* = 335.3, CF_3), 87.01 (dd, *J* = 194.9, 17.8 Hz, C-6), 86.6 (dd, *J* = 187.7, 18.2, C-2), 85.8-84.1 (m, C-3, 5), 68.2 (C-1), 26.4 (t, *J* = 23.6, C-4); ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.5 (CF_3), -198.6 (ddd, *J* = 49.6, 13.3, 3.2, F-3, 5), -203.4 (dd, *J* = 24.5, 13.0, F-1), -206.4 (dd, *J* = 24.6, 13.6, F-6) ; IR: ν_{max}/cm^{-1} 2935.66 (C-H), 1398.39 (C-F), 1203.58 (C-O), 1132.21 (S=O), 111.93 (S=O), 1035 (C-F); FTMS (ESI$^+$) m/z calcd for ([M]-Tf) 247.0746; found 247.0749 (Δ 1.2 ppm);

***N*-((2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-phenylcyclohexyl)acetamide (2.13)**



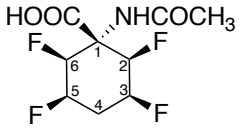
H_2SO_4 (1 mL) was added to a solution of benzyl bromide **2.1** (400 mg, 1.29 mmol) in MeCN (200 ml). The reaction mixture was stirred for 10-40 h at 90 °C until TLC analyses indicated the consumption of the starting material. After cooling to r.t., the mixture was poured into water (200 mL), extracted with EtOAc (3 × 200 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, followed by column chromatography purification using silica gel (petrol ether/ EtOAc 6:4) furnishing compound **2.13** (254 mg, 0.88 mmol, 68%); M.p.= 282 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.73 (2H, dt, *J* = 7.7, 1.1, Ar), 7.41 (2H, td, *J* = 8.0, 7.3, 1.8, Ar), 7.34 (1H, tt, *J* = 7.4, 2.0, Ar), 6.07- 5.90 (2H, m, H-2, 6), 5.43-5.20 (2H, m, H-3, 5), 2.57-2.47 (2 H, m, H-4), 1.82 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CD_3)_2CO$): δ 169.5 (C=O), 139.3 (Ar), 128.2 (Ar), 127.6 (Ar), 126.9 (Ar), 88.2 (dm, *J* = 205.7 Hz, C-2, 6), 86.1 (dm, *J* = 180.5 Hz, C-3, 5), 60.7 (C-1) , 26.8 (t, *J* = 22.3, C-4), 22.9 (CH_3); ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ -197.0 (AA'), -208.7 (BB'); IR: ν_{max}/cm^{-1} 3257 (N-H), 3217 (N-H), 3057 (C-H), 3001 (C-H), 1683 (C=O), 1559 (C-C); FTMS (ESI$^-$) *m/z* calcd for ([M]-H$^+$) 288.1011; found 288.1018 (Δ 2.4 ppm).

(2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-phenylcyclohexanamine (2.15) and (1*S*,2*R*,3*S*,4*R*,6*S*)-2-amino-3,4,6-trifluoro-2-phenylcyclohexanol (2.14.a)



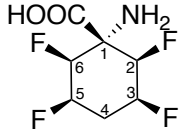
Compound **2.13** (50 mg, 0.17 mmol) was heated in aqueous HCl (10 mL of 6 M solution) at 120 °C for 18 h. The reaction was cooled to r.t and the solution was concentrated under reduced pressure. ^{19}F NMR of crude reaction mixture showed the ratio of **2.14.a** to **2.15** was 3:2. The aqueous mixture was loaded onto a reverse phase cartridge (1000 mg Extract Clean C18-HC, preconditioned with water), washed with water (10 mL), and the product eluted with water: MeCN (50:50) (3 × 10 mL). The eluted fractions were combined and concentrated. The residue was dissolved in MeCN: water (40:60) and purified by semipreparitive HPLC on the Shimadzu system (Phenomenex Luna C18 (250 × 10.00 mm, 5µ); mobile Phase: A (H_2O + 5% MeCN), B (MeCN); isocratic conditions: 50% B, flow rate: 10 mL. min^{-}1; detection 215 nm. Fractions containing products **2.14.a** (tR = 21.5 min) and **2.15** (tR = 23.5 min) were concentrated under reduced pressure to eliminate MeCN and freeze dried from frozen solutions in water, to offer **2.14.a** (6 mg, 0.025 mmol, 15 %) as white crystalline solid: M.p.= 170 °C; ^{1}H NMR (300 MHz, MeOD): δ 7.60 (2H, d, *J* = 7.9, Ar), 7.37 (2H, dd, *J* = 8.5, 6.7, Ar), 7.33-7.21 (1H, m, Ar), 5.39-5.19 (1H, m, H-5), 5.03-4.94 (1H, m, H-3), 4.62 (1H, dd, *J* = 49.9, 7.3, H-6), 4.40 (2 H, dd *J* = 14.5, 8.4, 2.2, H-2), 2.61-2.41 (1H, m, H-4a), 2.33-2.04 (1H, m, H-4b); ^{13}C NMR (126 MHz, MeOD): δ 143.4(Ar) , 127.8 (Ar), 126.7 (Ar) , 126.4 (Ar), 93.7 (dd, *J* = 182.2, 15.8, C-6), 90.7 (dd, *J* = 172.7, 16.7, H-3), 87.8-85.2 (m, H-5), 71.9 (d, *J* = 18.7, H-2), 60.5 (C-1), 30.5 (td, *J* = 21.2, 4.4, C-4); ^{19}F NMR (282 MHz, MeOD): δ -191.3 (d, *J* = 5.3, F-3), -198.3 (dd, *J* = 15.1, 5.2, F-5), -208.2 (d, *J* = 15.1, F-6); IR: ν_{max}/cm^{-1} 3451.1 (N-H), 3246.20 (O-H), 2866.84 (C-H), 1539.2 (C=C), 1072 (C-N); FTMS (ESI^{+}) *m/z* calcd for ([M]+H^{+}) 246.1105; found 246.1103 (Δ 0.8 ppm); followed by **(2.15)** (15 mg, 0.06 mmol, 35%) as white crystalline solid**:** M.p.= 159-160 °C; ^{1}H NMR (300 MHz, MeOD): δ 7.65 (2H, d, *J* = 7.3, Ar), 7.40 (2H, dd, *J* = 8.4, 6.9, Ar), 7.34-7. 26 (1H, tt, *J* = 7.3, 1.3, Ar), 5.49-5.03 (4H, m, H-2, 3, 5, 6), 2.67-2.31 (2H, m, H-4); ^{13}C NMR (126 MHz, MeOD): δ 143.5 (Ar), 128.1 (Ar), 127.0 (Ar), 125.7 (Ar), 90.0 (dd, *J* = 194.5, 16.8, C-2, 6), 86.5 (dm, *J* = 188.6, C-3, 5), 58.5 (C-1), 27.1 (t, *J* = 23.4, C-4); ^{19}F NMR (282 MHz, MeOD): δ -198.3 (AA'), -206.9 (BB'); IR: ν_{max}/cm^{-1} 3580 (N-H), 2916 (C-H), 2849 (C-H), 1653 (N-H), 1111 (C-F), 1028 (C-F); FTMS (ESI^{+}) *m/z* calcd for ([M]+Na^{+}) 270.0881; found 270.0875 (Δ 2.2 ppm);

(2*R*,3*S*,5*R*,6*S*)-1-(acetylamino)-2,3,5,6-tetrafluorocyclohexanecarboxylic acid (2.21)



$RuCl_3$ (5 mg, 0.026 mmol, 0.05 eq.) was added to a solution of acetomide **2.13** (150 mg, 0.52 mmol) and periodic acid H_5IO_6 (1 g, 4.4 mmol) in 14 mL of AcCN/$CC1_4$/H_2O (2:2:3) solvent system, followed by reflux for 18 h. After the reaction mixture was cooled down, the solvent mixture was concentrated and the crude product was redissolved in EtOAc and washed with H_2O and the aqueous layer was then extracted with EtOAc (200 mL x 2). Collected organic layers were dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude mixture has been dissolved in minimum amount of H_2O/MeCN solvent mixture and then was loaded onto a reverse phase cartridge (1000 mg Extract Clean C18-HC, preconditioned with H_2O), washed with H_2O (10 mL), and the product eluted with H_2O: MeCN (50:50) (2 × 10 mL) resulting in compound **2.21** (80 mg, 0.31 mmol, 61%): M.p.= 209-210 °C; ^{1}H NMR (500 MHz, $(CD_3)_2CO$): *δ* 4.21 (2H, d, *J* = 41.2, H-2, 6), 3.83- 3.52 (2H, m, H-3, 5), 1.23-1.10 (2H, m, H-4), 0.70 (3H, s, (CH_3)); ^{13}C NMR (126 MHz, $(CD_3)_2CO$): *δ* 170.9 (C=O), 167.0 (C-1) , 85.4 (d, *J* = 146.8, C-2, 6), 83.8 (d, *J* = 131.6, C-3, 5), 25.2 (t, *J* = 22.4, C-4), 20.0 (CH_3); ^{19}F NMR (376 MHz, $(CD_3)_2CO$): *δ* -199.2 (AA'), -211.7 (BB'); IR: ν_{max}/cm^{-1} 3273 (N-H), 2987 (C-H), 1662 (C=O), 1374 (C-H); FTMS (ESI^-) *m/z* calcd for ($[M]-H^+$) 256.0596; found 256.0601 (Δ 1.9 ppm);

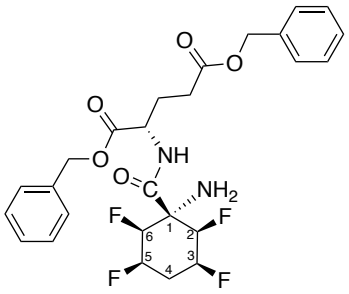
(2*R*,3*S*,5*R*,6*S*)-1-amino-2,3,5,6-tetrafluorocyclohexanecarboxylic acid(2.22)



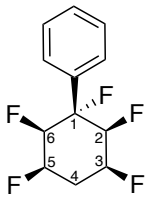
Compound **2.21** (70 mg, 0.27 mmol) has been heated in aqueous HCl (10 mL of 6 M solution) at 120 °C for 18 h. The reaction was cooled down to r.t and the solution was concentrated under reduced pressure. The crude mixture has been dissolved in minimum amount of H_2O solvent mixture and then was loaded onto a reverse phase cartridge (1000 mg Extract Clean C18-HC, preconditioned with H_2O), washed with H_2O (10 mL), and the product eluted with H_2O: MeCN (70:30) (3 × 10 mL) resulting in compound **2.22** (32 mg, 0.15 mmol, 55%): M.p.= 198-199 °C; ^{1}H NMR (500 MHz, MeOD): *δ* 5-20-4.95 (4H, m, H-2, 3, 5, 6), 2.57-2.45 (1H, m, H-4a), 2.41- 2.22 (1H, m, H-4b); ^{13}C NMR (126 MHz, MeOD): *δ* 171.7 (COOH), 88.3 (dd, *J* = 191.8, 17.5), 85.4 (dt, *J* = 182.0, 15.1), 28.8 (C-1), 27.4 (t, *J* = 22.1); ^{19}F NMR (282 MHz, MeOD): *δ* -200.3 (F-2, 6), -209.8 (F-3, 5); IR: ν_{max}/cm^{-1} 3133 (N-H), 3034 (N-H), 1727 (C=O), 1324 (C-O), 1069 (C-N); FTMS (ESI^-) *m/z* calcd for ($[M]-H^+$) 214.0491; found 214.0493 (Δ 0.9 ppm);

Dibenzyl(2*S*)-2-((((2*R*,3*S*,5*R*,6*S*)-1-amino-2,3,5,6 tetrafluorocyclohexyl)carbonyl)amino)pentanedioate (2.25)

EDCI hydrochloride (30 mg, 0.2 mmol) and N-Methylmorpholine (NMM) (mg, 0.6 mmol) were added to a solution of amino acid **2.22** (32 mg, 0.15 mmol) and HOBt (20 mg, 0.2 mmol) in dry DMF (2 mL) and the solution was stirred for 5 min at 0 °C. L-Glutamic acid dibenzyl ester hydrochloride (100 mg, 0.2 mmol) was the added and the solution was stirred at room temperature for 16 h. The reaction was diluted by sat ammonium chloride solution (10 mL), stirred for 1 h and then extracted into ethyl acetate (2 × 30 mL). The organic layer was washed with $NaHCO_3$ 10% (10 mL), and brine (10 mL), dried and then the organic solvent was evaporated under reduced pressure. The product was purified over silica gel using by ethyl acetate / petrol (1:1) as an eluent, to afford peptide **2.25** as a colourless liquid (30 mg, 0.057 mmol, 38%): M.p.= 195 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.32 (10H, m, Ar), 5.20 (2H, q, *J* = 12.2, CH_2-Ar), 5.12 (2H, s, CH_2-Ar), 5.09-4.94 (2H, m, H-2, 6), 4.85- 4.61 (3H, m, H-3, 5, C**H**-NH), 2.71- 2.57 (2H, m, C**H$_2$**CH_2CH), 2.54-2.31 (4H, m, H-4a, CH_2C**H$_2$**CH), 2.21-2.05 (1H, m, H-4b); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.4 (C=O-O), 170.8 (C=O-O), 170.6 (C=O(NH)), 135.7 (Ar), 135.0 (Ar), 128.7 (Ar), 128.6 (Ar) , 128.4 (Ar) , 128.4 (Ar) , 128.3 (Ar) , 89.2 (dm, *J* = 186.3, C-2, 6), 85.7 (dm, *J* = 183.6, C-3, 5), 67.5 (CH_2-Ar) , 66.7 (CH_2-Ar), 63.9 (C-1), 52.6 (CH-NH) , 29.9 (CH_2**C**H_2CH) , 27.3 (t, *J*= 22.0, C-4), 26.6 (**C**H$_2$$CH_2$CH); ^{19}F NMR (376 MHz, $CDCl_3$): δ -197.0 (dd, *J* = 12.3, 4.7, F-2), -197.4 (dd, *J* = 12.6, 5.0, F-6), -204.7 (dd, *J* = 24.8, 12.5, F-3), -205.3 (dd, *J* =2 5.0, 12.7, F-5); IR: ν_{max}/cm^{-1} 3415.99, 3365.84 (N-H), 3069.08 (N-H), 2938.6 (C-H), 1733.07 (C=O), 1669.42 (C=O), 1525.72 (C=O), 1165.99 (C-O), 1021.33 (C-F); FTMS (ESI$^+$) *m/z* calcd for ([M]+Na$^+$) 547.1832; found 547.1814 0493 (Δ 3.3 ppm);

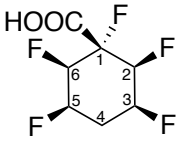


((2*R*,3*R*,5*S*,6*S*)-1,2,3,5,6-pentafluorocyclohexyl)benzene (2.26)



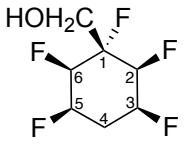
A solution of Tetrafluorocyclohexane bromide derivative **2.1** (800 mg, 25.81 mmol) and Ag(I)F (650 mg, 51.61 mmol) in Et_2O was refluxed for 18 h under Argon atmosphere and in light free conditions. Then the reaction mixture was cooled to r.t and filtered through short pad of celite and washed with Et_2O and concentrated under reduced pressure. Purification by column chromatography using silica gel (petrol ether/Et_2O 6:4) gave compound **2.26** (529 mg, 21.16 mmol, 82%): M.p.= 121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.67 (2H, m, Ar), 7.61-7.39 (3H, m, Ar), 5.30-4.79 (4H, m, H-2, 3, 5, 6), 2.89-2.66 (1H, m, H-4a), 2.65-2.41 (1H, m, H-4b); ^{13}C NMR (126 MHz, $CDCl_3$): δ 135.3 (*J* = 18.3, Ar), 129.8 (Ar) , 128.7 (Ar) , 125.7 (dt, *J* = 8.9, 4.1), 91.2 (d, *J* = 187.8 Hz, C-1), 87.7 (dm, *J* = 193.9, C-3, 5), 85.3 (dm, *J* = 185.9, C-2,-6), 26.3 (t, *J* = 22.0, C-4); ^{19}F NMR (376 MHz, $CDCl_3$): δ -166.6 (t, *J* = 13.6 Hz), -199.7 (dt, *J* = 8.2, 4.3), -213.5 (dd, *J* = 13.0, 7.9); IR: ν_{max}/cm^{-1} 2922.16 (C-H), 1452.4 (C=C), 1390.68 (C-F), 1336.67 (C-F), 1168.86 (C-F); FTMS (ESI$^-$) *m/z* calcd for ([M]-H$^+$) 249.0702; found 248.9907 (Δ 319 ppm);

(2*R*,3*R*,5*S*,6*S*)-1,2,3,5,6-pentafluorocyclohexanecarboxylic acid (2.27)



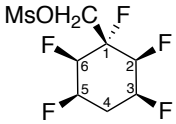
$RuCl_3$ (6 mg, 0.0295 mmol, 0.05 eq) was added to a solution of pentafluorocyclohexane **2.26** (150 mg, 0.59 mmol) and periodic acid H_5IO_6 (1.08 g, 4.72 mmol) in 14 mL of AcCN/$CC1_4$/H_2O (2:2:3) followed by reflux for 18 h. After the reaction mixture was cooled down, the solvent mixture was concentrated and the crude product was re dissolved in EtOAc and washed with H_2O and the aqueous layer was then extracted with EtOAc (200 mL x 2). Collected organic layers were dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude mixture has been dissolved in minimum amount of H_2O/MeCN solvent mixture and then was loaded onto a reverse phase cartridge (1000 mg Extract Clean C18-HC, preconditioned with H_2O), washed with H_2O (10 mL), and the product eluted with H_2O: MeCN (50:50) (2 × 10 mL) resulting in compound **2.27** (108 mg, 0.44 mmol, 74%): M.p.= 125 °C; ^{1}H NMR ^{1}H (500 MHz, MeOD): δ 5.29 (2H, dm, *J* = 44.0, H-2, 6), 5.03-4.95 (2H, m, H-3, 5), 2.54- 2.39 (2H, m, H-4^{a,b}); ^{13}C NMR (126 MHz, MeOD): δ 165.0 (s, COOH) , 124.7 (C-1), 85.0 (dm, *J* = 191.8, C-2, 3, 5, 6), 26.0 (t, *J* =22.1, C-4); ^{19}F NMR (376 MHz, MeOD): δ -174.4 (s(br), F-1), -200.8 (dt, *J* = 7.6, 3.9, F-2, 6), -215.8-216.7 (m, F-3, 5); IR: ν_{max}/cm^{-1} 2935.66 (O-H), 1730 (C=O), 1392.61 (C-F), 1296.16 (C-F); FTMS (ESI$^-$) *m/z* calcd for ([M]-H$^+$) 217.0287; found 217.0288 (Δ 0.5 ppm);.

((2*R*,3*R*,5*S*,6*S*)-1,2,3,5,6-pentafluorocyclohexyl)methanol (2.28):



To a solution of the pentafluorocyclohexane-1-carboxylic acid (**2.27**) (60 mg, 0.28 mmol) (246 mg, 1.5 mmol) in THF (3 mL) at 0 °C was added dropwise BH_3.THF (1M in THF, 1 mL, 1 mmol) dropwise. The reaction mixture was stirred at 50 °C for 18 h, after which it was quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc (2 x 30 mL). The combined organics were washed with brine (2 x 10 mL), dried (Na_2SO_4), and concentrated. The resulting material was purified by silica gel column chromatography (EtOAc/petrol ether 1:1) to provide the product **2.28** as white crystalline solid, which was found to sublime under reduced pressure (31 mg, 0.15 mmol, 55%): M.p.= 80 °C; ^{1}H NMR (400 MHz, $CDCl_3$: δ 4.99 (2H, d, *J* = 46.7, H-2, 6), 4.89- 4.67 (2H, m, H-3, 5), 4.16 (2H, ddt, *J* = 26.3, 6.4, 3.1, CH_2-OH), 2.74-2.57 (1H, m, H-4a), 2.52-2.41 (1H, m, H-4b); ^{13}C NMR (126 MHz, $CDCl_3$): δ 110.0 (d, *J*=213.5, C-1), 86.7- 82.9 (m, C-2, 3, 5, 6), 61.9 (d, *J* = 18.3, CH_2OH), 26.7 (t, *J* = 22.0, C-4); ^{19}F NMR (376 MHz, $CDCl_3$): δ -184.12 (s(br), F-1) , -199.8 (d, *J* = 44.0, F-2, 6), -215.7 (s (br), F-3,5); IR: ν_{max}/cm^{-1} 3290.56 (O-H), 2945.3 (C-H), 1716.66, 1622.13 (C=C), 1388.75 (C-F), 1267.23 (C-F), 1139.93 (C-O), 1026.13 (C-F); FTMS (ESI$^-$) *m/z* calcd for ([M]-H$^+$) 203.0495; found 203.0500 (Δ 2.5 ppm);

((2*R*,3*R*,5*S*,6*S*)-1,2,3,5,6-pentafluorocyclohexyl)methyl methanesulfonate (2.29):

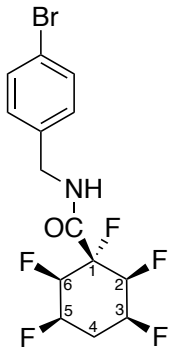


To a solution of pentafluoro alcohol **2.28** (32 mg, 0.12 mmol) in DCM (3 mL) at 0 C was added Et_3N (0.032 mL, 0.23 mmol) followed by $MeSO_2Cl$ (0.012 mL, 0.14 mmol). The reaction mixture was stirred at 0 °C for 30 min, then was allowed to warm to RT and left stirring over 18 h. The mixture was quenched with H_2O (5 mL) and extracted with DCM (2 x 10 mL). The combined organics were washed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated. The resulting material was purified by silica gel column chromatography (petroleum ether/ EtOAc 7:3) to provide the product as a colorless gum (21 mg, 0.076 mmol, 63 %): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.08-4. 78 (4H, m, H-2, 3, 5, 6), 4.71 (2H, dt, *J* = 24.7, 2.7, CH_2-O), 3.14 (3H, s, CH_3), 2.72-2.55 (1H, m, H-4a), 2.54-2.41 (1H, m, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$): δ 84.6 (dm, *J*= 186.8, C-2, 3, 5, 6), 66.8 (d, *J*= 18.2, CH_2-O), 37.8 (CH_3), 26.5 (t, *J*= 22.0, C-4); ^{19}F NMR (376 MHz, $CDCl_3$): δ -181.4 (s, F-1), -199.9 (s, F-2, 6), -214.5 (s, F-3, 5); IR: ν_{max}/cm^{-1} 3041.74 (C-H), 1357.89 (S=O), 1174.65 (C-O), 1128.36 (C-F), 1008.77 (C-F); FTMS (ESI$^+$) m/z calcd for ([M]+3H$^+$) 285.0583; found 285.0180 (Δ 141.3 ppm);

General coupling procedure for synthesis of compounds 2.34-2.37:

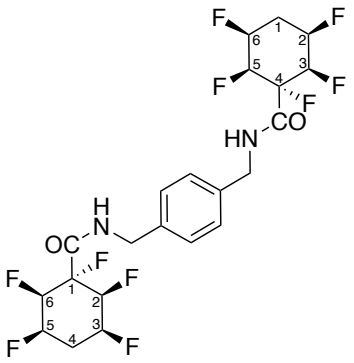
EDCI hydrochloride (1.3 eq) and N-Methylmorpholine (NMM) (4 eq.) were added to a solution of carboxylic acid **2.27** (1 eq.) and HOBt (1.3 eq.) in dry DMF and the solution was stirred for 5 min at 0 °C. An appropriate benzylamine (1.3 eq.) was the added and the solution was stirred at room temperature for 16 h. The reaction was diluted by sat ammonium chloride, stirred for 1 h and then extracted into ethyl acetate. The organic layer was washed with 10 % $NaHCO_3$ and brine, dried and then the organic solvent was evaporated under reduced pressure. The product was purified over silica gel chromatography by using EtOAc/ petrol ether solvent system as an eluent.

(2*R*,3*R*,5*S*,6*S*)-*N*-(4-bromobenzyl)-1,2,3,5,6-pentafluorocyclohexanecarboxamide (2.34):



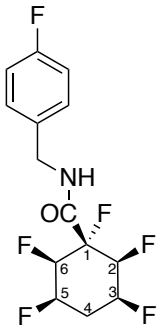
Following the general procedure above with **2.27** (100 mg, 0.46 mmol), HOBt (81 mg, 0.6 mmol), NMM (185 mg, 1.83 mmol), EDCI hydrochloride (114 mg, 0.6 mmol) and 4-Bromobenzylamine (**a**) (112 mg, 0.6 mmol), after purification using column chromatography (petroleum ether/ EtOAc 6:4) gave compound **2.34** (153 mg, 0.4 mmol, 87%) as white solid: M.p.= 143-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (2H, d, *J* = 8.4, Ar), 7.19 (2H, d, *J* = 8.5, Ar), 6.75 (1H, s, NH), 5.11 (2H, d, *J* = 45.9, H-3, 5), 5.01-4.72 (2H, m, H-2, 6), 4.55 (2H, d, *J* = 5.8, CH_2-Ar), 2.77- 2.55 (1H, m, H-4a), 2.58-2.41 (1H, m. H-4b); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.0 (CO) , 135.8 (Ar) , 132.0 (Ar) , 129.3 (Ar), 121.9 (Ar), 110.0 (C-1), 85.9 (dm, *J* = 155.2, C-3, 5), 84.2 (dm, *J* = 137.7, C-2, 6), 43.3 (CH_2-Ar), 26.2 (t, *J* = 22.2, C-4); ^{19}F NMR (376 MHz, $CDCl_3$): δ -174.8 (s (br), F-1) , -199.5 (dt, *J*=8.3, 4.5) (F-2,6), -(212.5-213.6) (m, F-3,5); IR: ν_{max}/cm^{-1} 3462.22 (N-H), 2956.87 (C-H), 2306.87, 1697.55 (C=O), 1529.55 (C=C), 1487.12 (C=C), 1114.86 (C-N), 1028.06 (C-F); FTMS (ESI^{+}) *m/z* calcd for ([M]+H^{+}) 386.0178; found 386.0172 (Δ 1.6 ppm);

(2*R*,3*R*,5*S*,6*S*)-1,2,3,5,6-pentafluoro-*N*-(4-(((((2*R*,3*R*,5*S*,6*S*)-1,2,3,5,6-pentafluorocyclohexyl)carbonyl)amino)methyl)benzyl)cyclohexanecarboxamide (2.35)



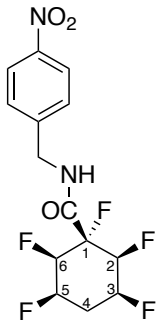
Following the general coupling procedure with **2.27** (30 mg, 0.138 mmol), HOBt (24 mg, 0.18 mmol), NMM (56 mg, 0.55 mmol), EDCI hydrochloride (35 mg, 0.18 mmol) and 1,4-Phenylenedimethanamine (**b**) (25 mg, 0.18 mmol), after purification using column chromatography (petroleum ether/ EtOAc 6:4) gave compound **2.35** (52 mg, 0.097 mmol, 70%) as white solid: M.p.= 178 °C; ^{1}H NMR (700 MHz, $(CD_3)_2CO$): δ 8.14 (2H, s(br), NH), 7.31 (4H, s, Ar), 5.45 (4H, d, J = 44.1 Hz, H-3, 5), 5.28-4.94 (4H, m, H-2, 6), 4.55 (4H, d, J = 6.0, CH_2Ar), 2.59-2.51 (1H, m, H-4a), 2.51-2.41 (1H, m, H-4b); ^{13}C NMR (176 MHz, $(CD_3)_2CO$): δ 163.2 (CO), 163.1 (CO) , 137.4 (Ar) , 127.5 (Ar), 110.0 (C-1) , 85.3 (dm, J = 189.1, C-2, 3, 5, 6), 42.8 (CH_2Ar), 26.3 (t, J = 43.2, C-4); ^{19}F NMR (659 MHz, $(CD_3)_2CO$): δ -171.3 (F-1) , -200.5 (d, J = 43.7, F-2, 6), -215.3 (F-3, 5); IR: ν_{max}/cm^{-1} 3469.94 (N-H), 3061.03 (C-H), 1716/64 (C=O), 1523.76 (C=C), 1128.36 (C-F), 1060.85 (C-F); FTMS (ESI$^+$) *m/z* calcd for ([M]+H$^+$) 537.1599; found 537.1587 (Δ 2.2 ppm);

(2*R*,3*R*,5*S*,6*S*)-1,2,3,5,6-pentafluoro-*N*-(4-fluorobenzyl)cyclohexanecarboxamide (2.36)



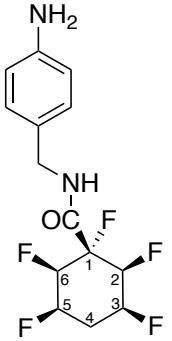
Following the general procedure above with **2.27** (10 mg, 0.046 mmol), HOBt (8 mg, 0.06 mmol), NNM (19 mg, 0.183 mmol), EDCI hydrochloride (11 mg, 0.06 mmol) and 4-Fluorobenzylamine (**c**) (10 mg, 0.07 mmol), after purification using column chromatography (petroleum ether/ EtOAc 7:3) gave compound **2.36** (9 mg, 0.026 mmol, 57%) as white solid: M.p.= 181-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.28 (2H, m, Ar) 7.07 (2H, dd, J = 17.8, 8.6, Ar), 6.72 (1H, s, NH), 5.12 (2 H, d, J = 47.2, H-3, 5), 4.98-4.71 (2H, m, H-2, 6), 4.57 (2H, d, J = 5.7, CH_2-Ar), 2.69-2.61 (1H, m, H-4a), 2.58-2.44 (1H, m, H-4b); ^{13}C NMR (126 MHz, $CDCl_3$): δ 195.6 (CO), 163.4 (d, J = 240.2, Ar), 132.5 (d, J = 3.1, Ar), 129.4 (d, J = 8.3, Ar), 115.8 (d, J = 21.5, Ar), 85.2 (dm, J = 16.6, C-3, 5), 84.3 (dm, J = 137.4, C-2, 6), 43.3 (CH_2-Ar), 29.7 (C-4); ^{19}F NMR (377 MHz, $CDCl_3$): δ -114.2 (F-Ar), -174.8 (F-1), -199.5 (dt, J = 8.2, 4.4, F-2, 6), -(210.2-214.8) (m, C-3, 5); IR: ν_{max}/cm^{-1} 3566.38 (N-H), 2922.16 (C-H), 2852.72 (C-H), 2358.94, 1716. 12(C=O), 1683(C=C), 1515.1 (C=C), 1338.6 (C-F); FTMS (ESI$^+$) *m/z* calcd for ([M]+H) 326.0979; found 326.0974 (Δ 1.5 ppm);

(2*R*,3*R*,5*S*,6*S*)-1,2,3,5,6-pentafluoro-*N*-(4-nitrobenzyl)cyclohexanecarboxamide (2.37)



Following the general procedure above with **2.27** (100 mg, 0.46 mmol), HOBt (81 mg, 0.6 mmol), NMM (185 mg, 1.83 mmol), EDCI hydrochloride (114 mg, 0.6 mmol) and 4-Nitrobenzylamine hydrochloride (112 mg, 06 mmol), after purification using column chromatography (petroleum ether/ EtOAc 6:4) gave compound **2.37** (130 mg, 0.37 mmol, 82 %) as white solid: M.p.= 156-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (2H, d, *J* = 9.2, Ar), 7.49 (2H, d, *J* = 9.2, Ar), 6.90 (1H, s, NH), 5.14 (2H, d, *J* = 47.2, H-3, 5), 5.03-4.76 (2H, m, H-2, 6), 4.72 (2H, d, *J* = 6.0, CH_2-Ar), 2.75-2.63 (1H, m, H-4a), 2.59-2.45 (1H, m, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.3 (CO), 148.3 (Ar) , 144.1 (Ar) , 128.1 (Ar), 124.1 (Ar), 110.0 (C-1) , 88.1-82.1 (m, C-2, 3, 5, 6), 43.2 (CH_2-Ar) , 26.3 (t, *J* = 22.6, C-4); ^{19}F NMR (376 MHz, $CDCl_3$): δ -174.7 (s(br), F-1), -199.5 (dt, *J* = 8.1, 4.3, F-2, 6), -212.5-212.7 (m, F-3, 5); IR: ν_{max}/cm^{-1} 3296.35 (N-H), 2360.87, 2343.51, 1681 (C=O), 1558.48 (N-O), 1519 (C=C), 1248.24 (C-F); FTMS (ESI$^+$) *m/z* calcd for ([M]+H) 353.0924; found 353.0914 (Δ 2.8 ppm);

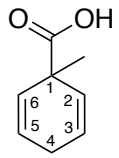
(2R,3R,5S,6S)-N-(4-aminobenzyl)-1,2,3,5,6-pentafluorocyclohexanecarboxamide (2.38)



To a solution of carboxamide **2.37** (20 mg, 0.057 mmol) in EtOAc (10 mL) was added $SnCl_2.2H_2O$ (38 mg, 0.17 mmol). The reaction mixture was stirred at 90 °C overnight. The mixture was filtered through celite, and the filtrate was washed with 10% $NaHCO_3$. The layers were separated and the aq. layer was further extracted with EtOAc. The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to provide the product as yellow solid **2.38** (11 mg, 0.037 mmol, 65%): M.p.= decomposed at 250 °C; ^{1}H (400 MHz, MeOD): δ 7.09 (2H, d, *J* = 8.2, Ar), 6.72 (2H, d, *J* = 8.1, Ar), 5.28 (2H, d, *J* = 46.7, H-3, 5), 5.05-4.80 (2H, m, H-2, 6), 4.39 (2H, s, CH_2-Ar), 2.62-2.40 (2H, m, H-4); ^{13}C NMR (126 MHz, MeOD): δ 164.2 (CO), 146.4 (Ar), 128.2 (Ar) , 127.3 (Ar) , 115.4 (Ar), 100 (C-1), 85.0 (dm, *J* = 185.2, C-2, 3, 5, 6), 42.7 (CH_2-Ar) , 26.1 (t, *J* = 24.2, C-4); ^{19}F NMR (376 MHz, MeOD): δ -201.3 (s(br), F-1), -201.7 (s(Br), F-2, 6), -215.9 (s(br), F-3, 5); IR: ν_{max}/cm^{-1} 3462.22 (N-H), 2956.87 (N-H), 2360.87, 1697.55 (C=O), 1529.55 (C=C), 1114.86 C(-F), 1028.08 (C-F); FTMS (ESI$^+$) *m/z* calcd for ([M]+H) 323.1180; found 323.1168 (Δ 3.7 ppm);

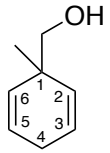
7.2.2. Chapter 3.

1-Methylcyclohexa-2,5-diene-1-carboxylic acid (3.2)[6]



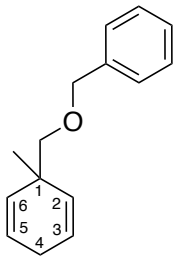
Liquid ammonia (200 mL) was added to benzoic acid **3.1** (12.2 g, 100 mmol) at -78 °C. Lithium (1.60 g) was then added in small portions until slowly dark blue colour persisted. After 2 h stirring at the -78 °C, iodomethane (56.1 g, 400 mmol) was added dropwise over a period of 5 min, during which the color gradually changed to yellow and ended up as pale yellow. Ammonia was evaporated, diluted HCl (400 mL) was slowly added and extracted with diethyl ether (200 mL x 3). The combined organic phases were washed with sodium sulfite (200 mL x 2) and water (300 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting pale yellow oil was used without further purification (12.5 g, 91 mmol, 91%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.89-5.85 (2H, m, H-3, 5), 5.32-5.78 (2H, m, H-2, 6), 2.67-2.69 (2H, s, H-4), 1.39 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 181.3 (COOH), 128.1 (C-3, 5), 125.0 (C-2, 6), 60.5 (C-1), 25.9 (C-4), 14.2 (CH_3); IR: ν_{max}/cm^{-1} 3354 (O-H), 1653 (C=O), 1394 (C-O).

((1-methylcyclohexa-2,5-dien-1-yl)methanol (3.3)[6]



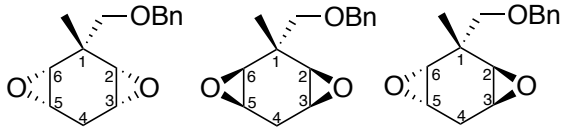
A solution of acid **3.2** (6.017 g, 48.3 mmol) in THF (80 mL) was added dropwise at –78 °C to a suspension of lithium aluminium hydride (1.9 g, 50 mmol) in THF (160 mL). The reaction mixture was allowed to warm to rt and stirring was continued for 16 h. The reaction was quenched with H_2O (200 mL) and diluted 2M HCl (10 mL). After stirring for another 30 min., the suspension was extracted with EtOAc (100 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to offer light yellow oil (4.97 g, 40.09 mmol, 83%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.94-5.90 (2H, m, H-3, 5), 5.49-5.45 (2H, m, H-2, 6), 3.34 (2H, s, CH_2), 2.68-2.66 (2H, m, H -4), 1.02 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 131.0 (C-3, 5), 126.3 (C-2, 6), 70.9 (C-1), 53.4 (CH_2), 26.5 (C-4), 24.8 (CH_3); IR: ν_{max}/cm^{-1} 3344 (O-H), 3061 (=C-H), 2924 (C-H), 1448 (C-H), 1026 (C-O).

(((1-methylcyclohexa-2,5-dien-1-yl)methoxy)methyl)benzene (3.4) [6]



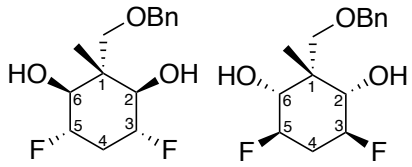
Alcohol **(3.3)** (2.5 g, 20.16 mmol) was added to a suspension of NaH (0.58 g, 24.19 mmol) in THF (10 mL) at rt. The mixture was stirred for 1 h at room temperature, then benzyl bromide (4.138 g, 24.19 mmol) was added. After overnight stirring, the mixture was quenched with sat. NH_4Cl (50 mL) and extracted with DCM (50 mL x 3). The combined extracts were dried over $MgSO_4$, filtered and solvent was removed under reduced pressure. The product was purified by column chromatography (petrol ether/DCM 9.5:0.5 to 9:1) to furnish the ether **3.4** (3.45 g, 16.12 mmol, 80%) as colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.36-7.28 (5H, m, Ar), 5.80-5.77 (2H, m, H-3, 5), 5.62-5.59 (2H, dt, *J* = 10.4, 2.0 Hz, H-2, 6), 4.56 (2H, s, Ph-CH_2), 3.25 (2H, s, O-CH_2), 2.68-2.66 (2H, m, H-4), 1.08 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.8 (Ar) 132.1 (C-3), 128.3 (Ar), 127.4 (C-2), 127.3 (Ar), 123.9 (Ar), 77.3 (Ph-CH_2), 73.3 (O-CH_2), 37.6 (C-1), 26.5 (C-4), 25.7 (CH_3); IR: ν_{max}/cm^{-1} 3030 (C-H), 2900 (C-H), 1456 (C-C), 1026 (C-O).

(1*R*,3*S*,5*R*,7*S*)-2-((benzyloxy)methyl)-2-methyl-4,8-dioxatricyclo[5.1.0.0^{3,5}]octane (3.5.a), (1*R*,3*S*,5*R*,7*S*)-2-((benzyloxy)methyl)-2-methyl-4,8-dioxatricyclo[5.1.0.0^{3,5}]octane (3.5.b) and (1*R*,3*R*,5*S*,7*S*)-2-((benzyloxy)methyl)-2-methyl-4,8 dioxatricyclo[5.1.0.0^{3,5}]octane (3.5.c)[7]



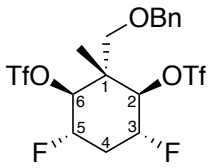
*m*CPBA (3.363 g, 19.5 mmol) was added to a solution of diene **3.4** (1.816 g, 8.47 mmol) in CH_2Cl_2 (200 mL) at 0 °C. The reaction mixture was allowed to warm to rt and was stirred for 14 h. The white precipitate was filtered and the filtrate washed with 10% aq. KOH, (100 mL). The aqueous layer was then extracted with DCM (100 mL x 3). The combined organic layers were washed with water (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a colourless crystalline solid, containing three diastereoisomers of diepoxide (**3.5.a**, **3.5.b** and **3.5.c**) as indicated by ^{1}H NMR spectrum in a ratio of 6: 4: 1. The crude product was then purified by silica gel column chromatography (EtOAc/hexane 9.5:0.5, 9:1, 7.5:2.5) to give trans diepoxide **3.5.c** as a colourless oil, (0.1472 g, 0.59 mmol, 7.1%)**;** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.24 (5H, m, Ar), 4.67-4.55 (2H, m, O-CH_2), 3.58 (1H, d, *J* = 8.8 Hz, Ph-CH_{2a}), 3.47 (1H, d, *J* = 8.8 Hz, Ph-CH_{2b}), 3.10 (2H, dddt, *J* = 8.5, 5.1, 3.3, 1.5 Hz, H-3, 5), 2.85 (2H, ddd, *J* = 30.5, 6.0, 1.9 Hz, H-2, 6), 2.31 (2H, m, H-4), 1.28 (3H, s, CH_3); followed by a mixture of diastereoisimers **3.5.a** and **3.5.b** as yellow oil (1.042 g, 4.24 mmol, 50%). **3.5.a** *(major)*: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.28 (5H, m, H-Ar), 4.64 (2H, s, O-CH_2), 3.72 (2H, s, Ph-CH_2), 3.16 (2H, ddd, *J* = 4.2, 2.9, 1.3 Hz, H-3, 5), 2.95 (2H, d, *J* = 4.0 Hz, H-2, 6), 2.77 (1H, dt, *J* = 17.2, 1.3 Hz, H-4a), 2.24 (1H, m, H-4b), 1.27 (3H, s, CH_3)**; 3.5.b** *(minor)***:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.28 (5H, m, Ar), 4.55 (2H, s, O-CH_2), 3.50 (2H, s, Ph-CH_2), 3.21 (2H, ddd, *J* = 4.1, 2.8, 1.3 Hz, H-3, 5), 2.91 (2H, d, *J* = 3.9 Hz, H-2, 6), 2.69 (1H, dt, *J* = 16.9 Hz, H-4a), 2.21 (1H, m, H-4b), 1.29 (3H, s, CH_3).

(1*R*,2*s*,3*S*,4*S*,6*R*)-2-((benzyloxy)methyl)-4,6-difluoro-2-methylcyclohexane-1,3-diol (3.6.a) and (1*R*,2*r*,3*S*,4*S*,6*R*)-2-((benzyloxy)methyl)-4,6-difluoro-2-methylcyclohexane-1,3-diol (3.6.b)[7]

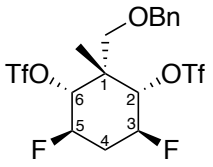


$Et_3N.3HF$ (5.1 g, 31.6 mmol) was added to a mixture of diepoxides **3.5.a** and **3.5.b** (0.974 g, 3.9 mmol) placed in a dry Teflon flask at room temperature. After 12 h stirring at 130 °C, the mixture was cooled to room temperature, poured into $NaHCO_3$ (20 mL) and extracted with DCM (20 mL x3). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure to give a 5:4 ratio mixture of 2 diastereomers, **3.6.a** and **3.6.b** (1.37 g, 4.76 mmol) as yellow oil; **3.6.a** (*major*): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.31 (10H, m, Ar), 4.98 (2H, m, H-3, 5), 4.50 (2H, s, O-CH_2), 3.57 (2H, s, Ph-CH_2,), 3.50 (2H, dd, *J* = 15.2, 9.1 Hz, H-2, 6), 2.59 (1H, m, H-4a), 1.73 (1H, m, 2.54, H-4b), 1.22 (3H, s, CH_3); ^{19}F NMR observe with ^{1}H decoupling (471 MHz, $CDCl_3$): δ -183.7 (2F, s, F-3, 5)**; (3.6.b)** *(minor)***:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.31 (10H, m, Ar), 4.53 (2H, m, H-3, 5), 4.58 (2H, s, O-CH_2), 3.80 (2H, dd, *J* = 13.5, 9.3 Hz, H-2, 6), 3.55 (2H, s, Ph-CH_2), 2.59 (2H, m, H-4a), 1.73 (1H, m, 2.54, H-4b), 0.90 (3H, s, CH_3); ^{19}F NMR observe with ^{1}H decoupling (471 MHz, $CDCl_3$) δ -190.7 (2F, s, F-3, 5).

(1*R*,2*s*,3*S*,4*S*,6*R*)-2-((benzyloxy)methyl)-4,6-difluoro-2-methylcyclohexane-1,3-diyl bis(trifluoromethanesulfonate) 3.7.a and (1*R*,2*r*,3*S*,4*S*,6*R*)-2-((benzyloxy)methyl)-4,6-difluoro-2-methylcyclohexane-1,3-diyl bis(trifluoromethanesulfonate) 3.7.b[7]



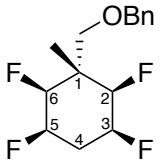
Trifluoromethanesulfonic anhydride (4.03 g, 14.27 mmol) was slowly added to a mixture of **3.6.a** and **3.6.b** (1.731 g, 6.03 mmol) in pyridine (15 mL, 186 mmol) at 0°C. After 18 h stirring at rt, the reaction mixture was quenched with a mixture of water (50 mL) and $CuSO_4$ (2 mL) and extracted with diethyl ether (50 mL x 3). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by means of column chromatography (petroleum ether/DCM 7:3) to offer



3.7.a (0.998 g, 1.809mmol, 30%) as white crystalline solid; M.p. = 87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.30 (5H, m, Ar), 5.46-5.18 (2H, m, H-3, 5), 4.77 (2H, dd, *J* = 13.4, 9.1 Hz, H-2, 6), 4.54 (2H, s, Ph-CH_2), 3.47 (2H, s, O-CH_2), 2.88-2.66 (1H, m, H-4a), 1.96-1.75 (1H, m, H-4b), 1.58 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 136.1 (Ar) 128.8 (Ar), 128.5 (Ar), 127.8 (Ar), 118.4 (q, *J* = 319.6 Hz, CF_3), 89.6 (d, *J* = 18.5 Hz, C-2, 6), 85.4 (dd, *J* = 181.1, 14.6 Hz, C-3, 5), 73.9 (O-CH_2), 67.4 (Ph-CH_2), 31.5 (t, *J* = 21.4 Hz, C-4), 29.1 (C-1), 20.1 (CH_3); ^{19}F NMR observe with ^{1}H decoupling (376 MHz, $CDCl_3$): δ -73.3 (6F, d, *J* = 13.4 Hz, OTf), -180.8 (2F, q, *J* = 13.9 Hz, F-3, 5); IR: ν_{max}/cm^{-1} 1417, 1404 (S=O), 1205 (C-F), 1139 (C-O), 842 (S-O); FTMS (ESI$^+$) *m/z* calcd for ([M]+Na) 573.0264; found 573.0247 (Δ 2.9 ppm); followed by **3.7.b** (0.93 g, 1.688 mmol, 28%) as thick oily liquid ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.30 (5H, m, Ar), 5.26 (2H, dd, *J* = 11.4, 9.6 Hz, H-2, 6), 4.95-4.71 (m, 2H, H-3, 5), 4.52 (s, 2H, OCH_2), 3.44 (2H, s, $PhCH_2$), 2.78-2.86 (1H, m, H-4b), 2.04-1.89 (1H, m, H-4a), 1.03 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 136.5 (Ar), 129.0 (Ar), 128.4 (Ar), 128.8 (Ar), 118.4 (q, *J* = 319.5 Hz, CF_3), 85.3 (dd, *J* = 181.0, 14.6 Hz, C-3, 5), 83.9 (d, *J* = 14.6 Hz, C-2, 6), 73.6 (CH_2), 68.2 (CH_2), 31.5 (t, *J* = 21.7 Hz, C-4), 29.1 (C-1), 22.6 (CH_3); ^{19}F NMR observe with ^{1}H decoupling (376 MHz, $CDCl_3$): δ -73.7 (6F, d, *J* = 12.1 Hz, CF_3), -189.5 (2F, q, *J* = 11.1 Hz, F-3, 5); ; IR: ν_{max}/cm^{-1} 1415, 1398 (S=O), 1203 (C-F), 1134 (C-O), 927 (S-O); FTMS (ESI$^+$) *m/z* calcd for ([M]+Na) 573.0264; found 573.0252 (Δ 2.1 ppm);

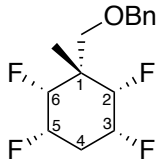
((((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)methoxy)methyl)benzene (3.8.a)[8]

A mixture of the triflate **3.7.a** (0.7012 g, 1.2 mmol) and $Et_3N.3HF$ (2.68 g, 16 mmol) were placed in Teflon round bottom flask equipped with condenser. After 48 h stirring at at 110°C, the mixture was cooled to rt, poured into $NaHCO_3$ (30 mL) and extracted with dichloromechane (20 mL x 3). Combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure, to give 0.45 g of brown solid. The product was purified by column chromatography (Petroleum ether/ DCM 75:25) to give **(3.8.a)** (0.169 g, 0.58 mmol, 34.8 %) as a white crystalline solid; M.p.= 78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.30 (5H, m, H-2', 3', 4'), 5.07 (2H, m, H-3), 4.75-4.62 (2H, dd, J=45.1, 17.0 Hz, H-2), 4.52 (2H, s, O-CH_2), 3.38 (2H, s, Ph-CH_2O), 2.71-2.50 (2H, m, H-4a), 2.12-1.90 (2H, m, H -4b), 1.59 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.2 (C-1'), 128.6 (C-2'), 128.1 (C-4'), 127.7 (C-3') 89.7 (d, *J* = 198.4 Hz, C-3), 87.0 (d, *J* = 180.2 Hz, C-2), 73.6 (CH_2), 71.6 (CH_2), 44.1 (C-1), 27.8 (C-4), 13.9 (CH_3); ^{19}F NMR observe with ^{1}H decoupling (377 MHz, $CDCl_3$): δ -193.9 (s br, F-3), -206.8 (s br, F-2); IR: ν_{max}/cm^{-1} 2960, 2891 (C-H), 1130, 1101 (C-O); FTMS (ESI$^+$) *m/z* calcd for ([M] +Na$^+$) 313.1190; found 313.1184 (Δ 1.9 ppm);

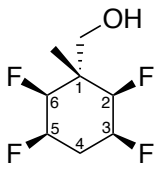


((((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)methoxy)methyl)benzene (3.8.b)[7]

Following the analogous method as described in synthesis of **3.7.a**, triflate **3.7.b** (0.3726 g, 0.675 mmol) furnished compound **3.8.b** (0.039 g, 0.135 mmol, 20.4 %) white crystalline solid; M.p = 83 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (5H, m, H-2',3',4), 4.87-4.63 (4H, m, H-2,3), 4.61 (2H,s, Ph-CH_2), 3.72 (2H, s br , O-CH_2), 2.76-2.58 (1H, m, H-4b), 2.41 (1H, dt, *J* = 11.0, 5.3 Hz, H-4b), 1.58 (3H, s, CH_3); ^{13}C NR (126 MHz, $CDCl_3$): δ 138.2 (C-1'), 128.4 (C-2'), 127.7 (C-4'), 127.6 (C-3'), 89.9 (d, *J* = 193.7 Hz, C-2), 85.8 (d, *J* = 185.8 Hz, C-3), 73.6 (Ph-CH_2), 70.8 (O-CH_2), 52.8 (C-1), 27.7 (t, *J* = 22.1 Hz, CH_2), 16.8 (CH_3); ^{19}F observe with ^{1}H decoupling NMR (471 MHz, $CDCl_3$): δ -195.2 (2F, **AA'**XX'), -207.6 (2F, AA'**XX'**); IR: ν_{max}/cm^{-1} 2985, 2891 (C-H), 1558, 1456 (C-C), 1082, 1018 (C-O); FTMS (ESI$^-$) *m/z* calcd for ([M]+Na$^+$) 313.1190; found 313.1182 (Δ 2.6 ppm);

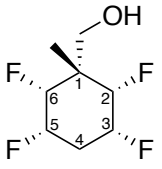


((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)methanol (3.9.a)[7]



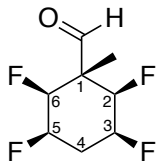
10% of Pd/C (0.02 g) was added to a solution of benzylated alcohol **3.8.a** (0.1696 g, 0.58 mmol) in ethyl acetate (5 mL). The mixture was degased, flushed three times with H_2 and left stirring under H_2 atmosphere at room temperature until completion (TLC monitoring). The reaction mixture was passed through a pad of celite. The filtrate was concentrated and purified using column chromatography (petrol ether/diethyl ether 75:25) resulting in **3.9.a** (0.064 g, 0.319 mmol, 55% yield) as a white crystalline solid; M.p.= 68 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.06 (2H, dm, *J* = 47.5 Hz, H-3, 5), 4.73-4.46 (2H, dd, *J* = 47.5, 22.3, 2.8 Hz H-2, 6), 3.60 (2H, s, CH_2), 2.66 (1H, dtq, *J* = 17.1, 11.5, 5.8 Hz, H-4a), 2.08-1.87 (1H, m, H-4b), 1.23 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 87.8 (d, *J* = 17.4 Hz, C-2, 6), 86.0 (d, *J* = 16.9 Hz, C-3, 5), 63.8 (CH_2), 40.8 (C-1), 28.4 (C-4),15.3 (CH_3); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$) δ -194.1-(-195.2) (s br , F-3, 5), -207.7 (s br , F-2, 6); IR: ν_{max}/cm^{-1} 3606 (O-H), 2958, 2891 (C-H), 1045 (C-F); (+CI) *m/z* calcd for ([M]- H$^+$) 199.1662; found 199.1605 (Δ 21.1 ppm);

((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)methanol (3.9.b)[7]



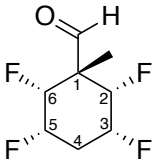
Following the analogous method as described in synthesis of **3.9.a,** benzylated alcohol **3.8.b.** (1.168 g, 0.57 mmol) was used instead to furnish **3.9.b** (0.068 g, 0.34 mmol, 59%) as a white crystalline solid**;** M.p.= 105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92-4.53 (4H, m, H-2, 3), 3.94 (2H, s, CH_2), 2.80-2.60 (1H, m, H-4a), 2.41 (1H, dt, *J* = 11.1, 5.6 Hz, H-4b), 1.02 (3H, t, *J* = 1.3 Hz, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 89.7 (dd, *J* = 189.7, 15.8 Hz, C-2), 85.7 (d, *J* = 185.2 Hz, C-3), 63.7 (t, *J* = 7.7 Hz, CH_2), 29.7 (C-1) 27.7 (t, *J* = 22.1 Hz, C-4), 16.3 (t, *J* = 6.3 Hz, CH_3); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -195.0 (2F, **AA'**XX'), -207.7-(-208.5) (2F, s br , AA'**XX'**);); IR: ν_{max}/cm^{-1} 3300 (O-H), 2956 (C-H); FTMS (ESI$^-$) *m/z* calcd for ([2M]-H$^+$) 399.1570; found 399.1575 (Δ 1.3 ppm);

(1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexane-1-carbaldehyde (3.10.a)[7]



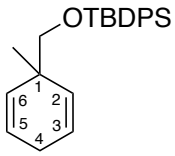
DMSO (10 mL) was added to a mixture of tetrafluoro alcohol (**3.9.a**), (0.134 g, 0.67 mmol) and IBX (1.3 g, 4.67 mmol) at rt. After stirring for 18 h at rt, water was added (30 mL) and extracted with diethyl ether (3 x 60 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure. Crude product was subjected to column chromatography (petroleum ether/diethyl ether 6:4) to give **3.10.a** (0.1195 g, 0.604 mmol, 90%) as white crystalline solid; M.p = 68-69°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (1H, t, *J* = 3.3 Hz, CHO), 5.07 (4H, m, H-2, 3, 5, 6), 2.65 (1H, m, H-4a), 2.27 (1H, m, H-4b), 1.63 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1 (COH), 90.4 (d, *J* = 205.1 Hz, C-3, 5), 85.2 (d, *J* = 204.6 Hz, C-2, 6), 30.9 (C-1), 27.0 (C-4), 13.3 (CH_3); ^{19}F NMR observe with ^{1}H decoupling (376 MHz, $CDCl_3$): δ -193.3 (s br , F-2, 3, 5, 6); IR: ν_{max}/cm^{-1} 1728 (C=O); TOF MS (EI$^+$) *m/z* calcd for ([M]) 198.0668; found 198.0671 (Δ 3.7 ppm);

(1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexane-1-carbaldehyde (3.10.b)[7]



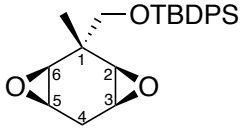
Following analogous method as in synthesis of **3.10.a***,* tetrafluoro alcohol (**3.9.b**) was used to furnish **3.10.b** (0.095 g, 0.48 mmol, 68%) as a white crystalline solid; M.p.= 78-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (1H, s, CHO), 4.88 (4H, m, H-2, 3, 5, 6), 2.80 (1H, dtt, *J* = 12.3, 9.2, 3.1 Hz, H-4a), 2.27 (1H, m, H-4b), 1.18 (3H, s br , CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.1 (CHO), 90.4 (d, *J* = 179.5 Hz, C-2, 6), 85.3 (d, *J* = 183.8 Hz, C-3, 5), 60.4 (CH_2), 41.3 (C-1), 28.2 (C-4), 15.7 (CH_3); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -195.5 (s br , F-3, 5), -205.1 (s br , F-2, 6); IR: ν_{max}/cm^{-1} 1730 (C=O); FTMS (ESI$^+$) *m/z* calcd for ([M]+Na$^+$) 221.0565; found 221.0557 (Δ 1.5 ppm);

Tert-butyl((1-methylcyclohexa-2,5-dien-1-yl)methoxy)diphenylsilane (3.11)



TBDPSCl (2.66 g, 9.68 mmol) was added to a solution of an alcohol **3.3** (1 g, 8.065 mmol), imidazole (1.64 g, 24.2 mmol) and Iodine (4 g, 16 mmol) in THF (20 mL). The reaction mixture and was left to stir at rt over night. Et.Ac. (50 mL) was added to the reaction mixture and washed with aqueous $Na_2S_2O_3$. Organic layers were combined, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (petrol ether/DCM 9:1) to afford compound **3.11** (1.949 g, 5.273 mmol, 65%) as colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.69 (4H, m, Ar), 7.57-7.37 (6H, m, Ar), 5.81 (2H, dtd, *J* = 10.5, 3.4, 1.7 Hz, H-2, 6), 5.64 (2H, dt, *J* = 10.4, 2.0 Hz, H-3, 5), 3.49 (2H, s, H-4a), 2.70 (2H, tt, *J* = 3.3, 2.1 Hz, H-4b), 1.18(3H, s, CH_3), 1.13 (9H, s, $(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.7 (Ar), 134.8 (Ar), 132.0 (C-2, 6), 129.5 (C-3, 5), 127.7 (Ar), 123.9 (Ar), 72.0 (CH_2), 38.6 (C-1), 26.9 $(CH_3)_3$), 26.7 (C-4), 25.2 (CH_3), 19.4 (C-$(CH_3)_3$; IR: ν_{max}/cm^{-1} 2958, 2929, 2856 (C-H), 1114, 1083 (C-O); FTMS (ESI$^+$) *m/z* calcd for ([M]+Na) 385.1963; found 385.1958 (Δ 1.3 ppm);

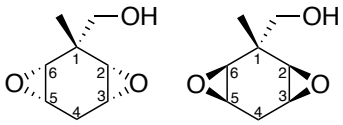
***tert*-butyl(((1*R*,2*s*,3*S*,5*R*,7*S*)-2-methyl-4,8-dioxatricyclo octan-2-yl)methoxy)diphenylsilane (3.12)**



*Following the proceedure described in synthesis of **3.5**: m*CPBA (60%) (2.6 g, 4.53 mmol), compound **3.11** (1.949, 5.27 mmol), DCM (200 mL) was used to give diepoxide **3.12** (1.438 g, 3.65 mmol, 69%) as yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.62 (4H, m, Ar), 7.54-7.35 (6H, m, Ar), 3.68 (2H, s, CH_2), 3.20 (2H, tt, *J* = 3.1, 1.3 Hz, H-2, 6), 2.94-2.83 (2H, m, H-3, 5), 2.71 (1H, d, *J* = 17.0, O-CH_{2a}), 2.27-2.21 (1H, m, O-CH_{2b}), 1.21 (3H, s, CH_3), 1.09 (9H, s, $(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) : δ 145.5 (C(Ar)), 135.7 (Ar), 129.9 (Ar), 129.7(Ar), 69.7 (CH_2), 57.3 (C-2, 6), 51.5 (C-3, 5), 26.9 ($(CH_3)_3$), 24.3 (C-$(CH_3)_3$), 23.4 (C-1), 18.1 (CH_3); IR: ν_{max}/cm^{-1} 2958, 2929, 2856 (C-H), 1105 (C-O-C); FTMS (ESI$^+$) *m/z* calcd for ([M]+Na$^+$) 417.1861, found 417.1854 (Δ 1.7 ppm);

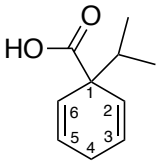
((1*R*,2*s*,3*S*,5*R*,7*S*)-2-methyl-4,8-dioxatricyclo-octan-2-yl)methanol 3.15.a and

((1*R*,2*r*,3*S*,5*R*,7*S*)-2-methyl-4,8-dioxatricyclo octan-2-yl)methanol 3.15.b



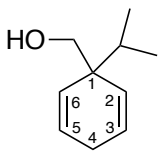
*Following the procedure described described in synthesis of **3.5**: m*CPBA (0.56 g, 2.265 mmol), diene **3.3** (0.094 g, 0.755 mmol), THF (30 mL) was used to generate products **3.14.a** and **3.14.b**, with the ratio of 6: 7.5 according to integration of CH_3 groups at position C-1 on crude ^{1}H NMR: **3.15.a:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97-3.57 (2H, m, O-CH_2), 3.20-2.81 (4H, m, H-2, 3, 5, 6), 2.45-2.10 (2H, m, H-4), 1.17 (3H, s, CH_3); **3.15.b:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97-3.57 (2H, m, O-CH_2), 3.20-2.81 (4H, m, H-2, 3, 5, 6), 2.45-2.10 (2H, m, H-4), 1.13 (3H, s, CH_3).

1-Isopropylcyclohexa-2,5-diene-1-carboxylic acid (3.17) [9]



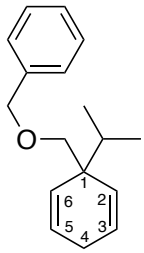
Diene 3.17, has been synthesized according to the literature procedure described by Linker et. al.[9] *as well as similar to the procedure described in synthesis of **3.2**.*[7,10] Benzoic acid **3.1** (12.2 g, 100 mmol), Lithium (1.6 g, 230 mmol), ispopropyl iodide (68 g, 400 mmol), NH_3 (400 mL) to furnish **3.17** (12.49 g, 76 mmol, 76%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98 (2H, dt, *J* = 10.4, 3.3 Hz, H -2, 6), 5.76 (2H, dt, *J* = 10.6, 2.1 Hz, 2H, H-3, 5), 2.74-2.55 (2H, m, H-4), 2.20-2.10 (1H, m, $CH(CH_3)_2$, 0.89 (6H, d, *J* = 6.9 Hz, -$(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) 181.0 (COOH), 126.8 (C-3, 5), 125.4 (C-2, 6), 51.9 (C-1), 35.7 (CH-$(CH_3)_2$), 26.5 (C-4), 17.4 ($(CH_3)_2$)); FTMS (ESI^+) *m/z* calcd for ([M]+Na^+) 189.0891, found 189.0886 (Δ 2.6 ppm);

(1-Methylcyclohexa-2,5-dien-1-yl)methanol (3.18) [11]



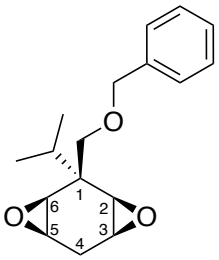
*Compound **3.18** has been previously prepared and reported in the literature by* Breit *et al, ^{1}H NMR has been compared and consistent with the literature NMR*.[11] Compound **3.17** (6.25 g, 38 mmol), $LiAlH_4$ (1.59 g, 42 mmol), THF (100 mL) were used to prepare **3.18** (4.97 g, 40.089 mmol, 85 %) as yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.04 (1H, dt, *J*=10.5, 3.3, H-3, 5), 5.45 (1 H, dq, *J* = 10.5, 2.1, H-2, 6), 3.47 (2H, s, CH_2-OH), 2.69-2.66 (2H, m, H-4), 1.61 (1H, sept, *J* = 6.9, CH-$(CH_3)_2$), 0.87 (6H, d, *J*=6.9 $(CH_3)_2$).

(((1-Isopropylcyclohexa-2,5-dien-1-yl)methoxy)methyl)benzene (3.19)



*Following the procedure described in synthesis of **3.4**:* Benzyl bromide (7.96 g, 47 mmol), compound **3.18** (5.55 g, 36 mmol), NaH (60%) (1.72 g, 43 mmol) furnished benzylated alcohol **3.19** (6.92 g, 28.6 mmol, 80%) as colourless oil*;* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.25 (5H, m, Ar), 5.97-5.83 (2H, m, H-3, 5), 5.57 (2H, dt, *J* = 10.5, 2.0 Hz, H-2, 6), 4.54 (2H, s, O-CH_2-Ar), 3.37 (2H, s, CH_2-OBn), 2.80 -2.54 (2H, m, H-4), 1.96-1.77 (1H, m, CH-$(CH_3)_2$, 0.85 (6H, d, *J* = 6.9 Hz, -$(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.9 (s, Ar), 129.4 (Ar), 128.3 (Ar), 127.4 (Ar), 127.3 (C-3, 5), 125.7 (C-2, 6), 76.5 (s, CH_2), 73.3 (s, CH_2), 44.0 (s, C-1), 32.8 (C-4), 27.1 (s, CH), 17.4 (s, CH_3); FTMS (ESI^+) *m/z* calcd for ([M]+K^+) 281.13077; found 281.1313 (Δ 1.3 ppm);

(1*R*,3*S*,5*R*,7*S*)-2-((benzyloxy)methyl)-2-(propan-2-yl)-4,8-dioxatricyclo octane (3.20)



*Following the procedure described in synthesis of **3.5**.* *m*CPBA (21 g, 86 mmol), compound **3.19** (6.9 g, 28.6 mmol), THF (100 mL) furnished diepoxide **3.20** (6.98 g, 25.5 mmol, 89%) as crystalline solid**;** M.p.= 144-145°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.25 (5H, m, Ar), 4.61 (2H, s, O-CH_2-Ar), 3.76 (2H, s, CH_2-OBn), 3.19 (2H, ddd, *J* = 4.1, 2.9, 1.3 Hz, H-2, 6), 3.02-2.95 (2H, m, H-3, 5), 2.74 (1H, m, H-4a), 2.29 (1H, m , H-4b), 2.19 (1H, dt, *J* = 17.2, 3.0 Hz, CH), 1.05 (6H, d, *J* = 7.1 Hz, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.5 (Ar), 133.5 (Ar), 128.3 (Ar), 127.6 (Ar), 73.6(s, CH_2), 70.8 (s, CH_2), 53.9 (C-3, 5), 50.6 (C-2, 6), 39.5 (C-1), 29.7 (CH), 23.5 (C-4), 17.2 $(CH_3)_2$; IR: ν_{max}/cm^{-1} 1310 (C-O), 1280 (C-O-C); MS (EI) *m/z* calcd for ([M]+Na^+) 297.1466, found 297.1454 (Δ 4.0 ppm);

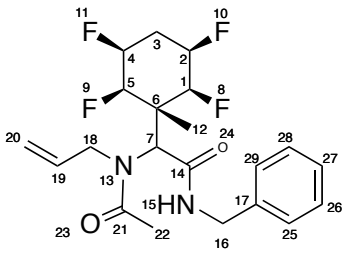
General procedure A for synthesis of compounds 3.23-3.40:[7]

Appropriate amine (**A1-2**) was added to a solution of the aldehyde (1 equiv.) in DCM and 0.1 equiv. of $MgSO_4$. The resulting mixture was stirred until complete condensation (TLC and ^1H NMR). A solution of the isocyanide (**B1-2**) (1.2 equiv.) in DCM (1 mL) and carboxylic acid (**C1-3**) (1.2 equiv.)) in DCM (1 M solution) were added to the reaction mixture and the resulting solution was allowed to stir at 35 °C for 24 hours. The solvent was evaporated, saturated NH_4Cl (10 mL) was added and the organic layer was extracted into ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo and purified by flash chromatography on silica gel and by HPLC.

General procedure B for synthesis of compounds 3.30, 3.39:[7]

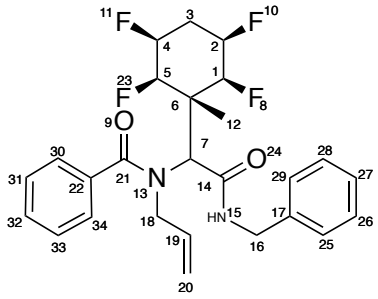
1.2 equiv. of an appropriate amine (**A1-2**) was added successfully to a solution of the aldehyde (1 equiv.) in DCM and 0.1 equiv. of $MgSO_4$. On the completion of the condensation (TLC and ^1H NMR), the primary solvent was evaporated using rotor evaporator and re-dissolved in methanol. A solution of an appropriate isocyanide (**B1-2**) (1.2 equiv.) in methanol, and a solution of carboxylic acid (**C1-3**) (1.2 equiv.) in methanol (1 M solution) were added subsequently and the resulting solution was allowed to stir at 35 °C for 24 hours. On completion, the solvent was evaporated, saturated NH_4Cl (10 mL) was added and the organic layer was extracted into EtOAc (3 x 10 mL). The combined organic extracts were then dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel and if required further by HPLC.

2-(N-allylacetamido)-N-benzyl-2-((1s,2R,3S,5R,6S)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)acetamide(3.23)

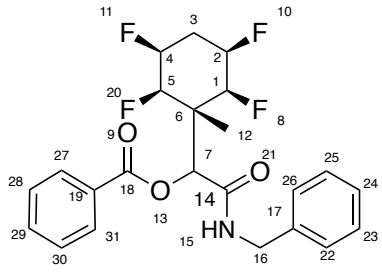


Following general procedure A using tetrafluoro aldehyde **3.10.a** (15 mg, 0.076 mmol) with an appropriate components (allylamine, *tert*-butyl isocyanide and acetic acid) after the purification using column chromatography (petroleum ether/ EtOAc 9:1, 6:4) furnished compound **3.23** (18 mg, 0.044 mmol, 58%) as white solid; M.p = 222-223°C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.27 (1H, s, NH), 7.33 (5H, m, H-25-29), 5.69 (dtt, *J* = 9.8, 7.5, 6.9, Hz, H-19), 5.20- 5.47 (2H, m, H-1, 5), 5.08 (1H, t, *J* = 1.7 Hz, H-20a), 5.05 (1H, dq, *J* = 7.2 , 1.7 Hz, H-20b), 4.88 (2H, m, H-2, 4), 4.62 (1H, d , *J* = 17.1 Hz, H-18a), 4.48 (1H, dd, *J* = 14.6, 6.1 Hz, H-16a), 4.33 (d, *J* = 10.3 Hz, H-18b) , 4.25 (1H, dd, *J* = 14.6, 5.4 Hz, H-16b), 2.41 (1H, m , H-3a), 2.29 (1H, m, H-3b), 2.15 (3H, s, H-22), 1.55 (3H, s, H-12); ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 173.5 (C-21), 172.2 (C-14), 149.9 (C-17), 135.1 (C-18), 128.5 (C-25, 29), 128 (C-26, 28), 127.3 (C-27), 114.8 (C-20), 90.1 (dd, *J* = 185.8, 18.3, Hz, C-1, 5), 86.5 (dd, *J* = 183.6, 25.6 Hz, C-2, 4), 54.1 (C-7), 53.8 (C-6), 49.3 (C-18), 43.1 (C-16), 26.8 (C-3), 21.6 (C-22), 12.5 (C-12); ^{19}F observe with ^{1}H decoupling NMR (101 MHz, $(CD_3)_2CO$): δ -193.1 (d, *J* = 14.6 Hz, F-2, 4), -196.1 (dd, *J* = 13.7, 5.3 Hz, F-1, 5); IR: ν max/cm^{-1} 3317 (N-H), 1680 , 1649 (C=O), 1066 (C-N), 921 (N-H); FTMS (ESI^{-}) *m/z* calcd for ([M]-H) 413.1852; found 413.1860 (Δ 1.9 ppm);

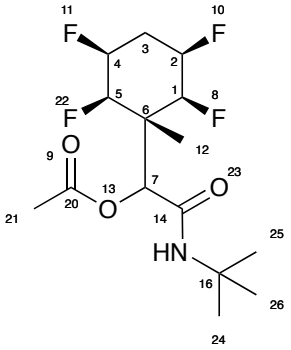
***N*-allyl-*N*-((*R*)-2-(benzylamino)-2-oxo-1-((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl)benzamide (3.24)**



Following general procedure A using 0.075 mmol. of tetrafluoro aldehyde **3.10.a** with an appropriate components (allylamine, benzyl isocyanide and benzoic acid). The crude product was purified by means of column chromatography (petroleum ether/ EtOAc 8:2) to offer **3.24** (9 mg, 0.019 mmol, 25%) as white crystalline solid; M.p. = 154-155°C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.49-7.21 (10H, m, H-(25-34)), 5.68-5.61 (1H, m, H-19), 5.56-4.51 (7H, m, H-1, 2, 4, 5, 7, 20), 4.42 (1H, dd, *J*=14.7, 6.1 Hz, H-16), 4.35-4.11 (3H, m, H-16b, H-18), 2.84-2.58 (1H, m, H-3a), 2.09-1.83 (1H, m, H-3b), 1.55 (3H, s, H-12); ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 174.4 (C-14), 168.3 (C-21), 136.9 (C-22), 135.8 (C-17), 133.6 (C-20), 130.2 (C-30, 34), 128.8 (C-31, 33), 128.5, (C-27), 127.9 (C-26, 28), 127.7 (C-32), 126.9 (C-25, 29), 90.0 (d, *J*=180.1, 22.2 Hz, C-1, 5), 86.64 (d, *J*=186.7, 20.1 Hz, C-2, 4) , 74.6 (C-7), 48.4 (C-6), 43.7 (C-16), 29.0 (C-3), 12.9 (C-12); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $(CD_3)_2CO$): δ -193.4 (s br , F-2, 4) , -195.9 (s br , F-1, 5); IR: ν_{max}/cm^{-1} 3323 (N-H), 1726 (C=O), 1687 (C=O), 1244 (C-N), 1020, 970 (C-F); FTMS (ESI$^+$) *m/z* calcd for ([M]+Na$^+$) 499.1984; found 499.1972 (Δ 2.9 ppm); followed by **(*R*)-2-(benzylamino)-2-oxo-1-((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1 methylcyclohexyl)ethyl benzoate (3.25)**: white solid (6 mg, 0.015 mmol, 20%); M.p.= 145-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.20 (10H, m, H-(22-31), 6.57 (1H, s, NH), 5.53 (1H, s, H-7), 5.20- 4.69 (4H, m, H-1, 2, 4, 5), 4.56 (1H, dd, *J*=15.0, 6.2 Hz, H-16a), 4.46 (1H, d, *J*=14.9, 5.7 Hz, H-16b), 2.81-2.61 (1H, m, H-3a), 2.21- 1.95 (1H, m, H-3b), 1.51 (3H, s, H-12); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.2 (C-14), 164.8 (C-18), 137.2 (C-17), 134.4 (C-29), 130.0 (C-27, 31), 129.0 (C-28, C-30), 128.9 (C-22, 26), 128.1 (C-19), 127.8 (C-24), 127.5 (C-23, 25), 89.1 (ddd, *J* = 190.7, 48.1 Hz, C-1, 5), 86.0 (dd, *J* = 186.3, 31.4 Hz, C-2, 4), 73.9 (C-7), 46.3 (C-6), 43.4 (C-16), 28.4 (C-3), 12.7 (C-12); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -194.6 (d, *J*= 7.8, Hz), -194.7 (d, *J* = 7.8, Hz); IR: ν_{max}/cm^{-1} 3271 (N-H), 2951 (C-H), 1732 (C=O), 1653 (C=O); FTMS (ESI$^+$) *m/z* calcd for ([M]+Na$^+$) 460.1512; found 460.1501 (Δ 2.4 ppm);

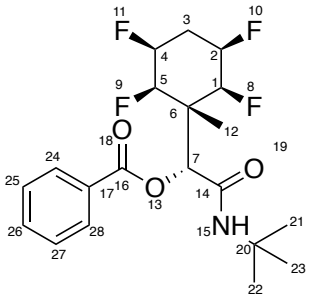


2-(*tert*-Butylamino)-2-oxo-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl acetate (3.26)



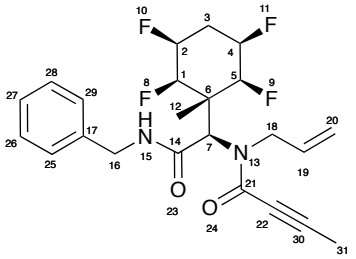
Following general procedure A using 0.05 mmol. of tetrafluoro aldehyde **3.10.a** with an appropriate components (allylamine, *tert*-butyl isocyanide and acetic acid). The crude product was purified by means of column chromatography (petroleum ether/ EtOAc 8:2) to furnish **3.26** (14 mg, 0.041 mmol, 82%) as yellow solid; M.p. = 169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (1H, s, NH), 5.21-4.62 (5H, m, H-1, 2, 4, 5, 7), 2.74 - 2.53 (1H, m, H-3a), 2.24 (3H, s, H-21), 2.23-2.09 (1H, m, H-3b), 1.41 (3H, s, H-12), 1.39 (9H, s, H-24, 25, 26); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8 (C-20), 165.8 (C-14), 89.1 (d, *J* = 190.0 Hz, C-1, 5), 85.9 (d, *J*=187.1 Hz, C-2, 4), 73.1 (C-7), 52.0 (C-16), 45.6 (C-6), 29.7 (C-3), 28.6 (C-24, 25, 26), 22.7, 20.8 (C-21), 12.9 (C-12); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -194.0 (s br , F-2, 4) , -194.4 (dd, *J* = 13.7, 6.9 Hz, F-1, 5); IR : ν max/cm^{-1} 3388 (N-H), 2919 (C-H), 1730, 1689 (C=O)**;** FTMS (ESI^{+}) *m/z* calcd for ([M]+Na) 364.1511; found 364.1495 (Δ 4.4 ppm);

(*R*)-2-(*tert*-butylamino)-2-oxo-1-((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl benzoate (3.27)

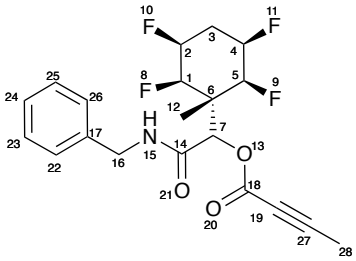


Following general procedure A using 0.05 mmol. of tetrafluoro aldehyde **3.10.a** with an appropriate components (allylamine, *tert*-butyl isocyanide and benzoic acid). The crude product was purified by means of column chromatography (petroleum ether/ EtOAc 7:3) to offer **3.27** (16 mg, 0.04 mmol, 79%) as white solid; M.p.= 178°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-7.48 (5H, m, H-(24- 28)), 6.02 (1H, s, NH), 5.29 (1H, s, H-7), 5.26- 4.70 (4H, m, H-1, 2, 4, 5), 2.68 (1H, m, H-3a), 2.21 (1H, m, H-3b), 1.51 (3H, s, H-12), 1.36 (9H, s, H-21-23); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0 (C-16), 164.5 (C-14), 134.4 (C-26), 129.8 (C-24, 28), 129.1 (C-27), 89.1 (d, *J* = 190.0 Hz, C-1,5), 85.9 (d, *J* = 185.5 Hz, C-2,4), 73.5 (C-6), 52.0 (C-20), 28.5 (C-21, 22, 23), 28.1 (C-3), 12.9 (C-5); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -194.2 (s br, -194.6 (dd, *J* = 13.4, 7.2 Hz); IR : ν max/cm^{-1} 3307 (N-H), 1653 (C=O), 1066 (C-N), 948 (N-H); FTMS (ESI^{+}) *m/z* calcd for ([M]+Na^{+}) 426.1668; found 426.1653 (Δ 3.5 ppm);

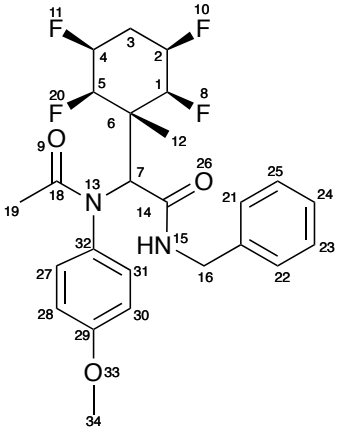
(S)-2-(benzylamino)-2-oxo-1-((1s,2R,3S,5R,6S)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl but-2-ynoate (3.28)



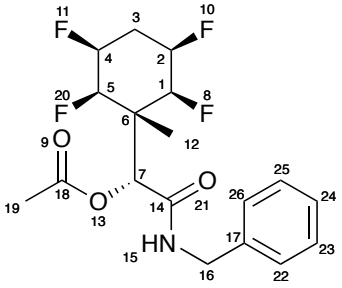
Following general procedure A using 0.05 mmol. of tetrafluoro aldehyde **3.10.a** with an appropriate components (allylamine, benzyl isocyanide and 2-butynoic acid). The crude product was purified by means of column chromatography (petroleum ether/ EtOAc 7:3) to offer **3.28** (5 mg, 0.011 mmol, 22 %) as white solid; M.p. = 198 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.29 (5H, m, C- 25-29), 6.39 (1H, s br , NH), 5.81-5.68 (1H, m, C-19), 5.18- 5.11 (2H, m, H-20), 5.09- 4.79 (4H, m, H-1, 2, 4, 5), 4.49 (1H, dd, *J* =14.7, 6.2 Hz, H-16a), 4.45-4.35 (3H, m, H-7, H-18), 4.15 (1H, dd, *J*=14.8, 4.9 Hz, H-16b), 2.63 (1H, s (br), H-3a), 2.11 -2.01 (1H, m, 3b), 2.01 (3H, s, H-31), 1.48 (1H, s, H-12); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.2 (C-14), 157.3 (C-21), 133.5 (C-19), 128.9 (C-26, 28), 128.7, 128.5 (C-17), 127.9 (C-25, 29), 127.7 (C-27), 117.9 (C-20), 92.8 (C-30), 89.9 (dd, *J* = 185.5, 32.7, Hz, C-1, 5), 84.3 (dd, *J* = 188.8, 31.1 Hz, C-2, 4), 73.3 (C-22), 64.8 (C-7), 48.4 (C-18), 43.8 (C-16), 29.7 (C-6), 23.4 (C-3), 12.8 (C-12), 4.0 (C-31); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -193.1 (s br), -195.9 (s br); IR: ν max/cm^{-1} 3307 (N-H), 3067, 2990 (C-H), 1690 (C=O), 1587 (C-C); FTMS (ESI^{+}) *m/z* calcd for ([M]+Na) 461.1828; found 461.1809 (Δ 4.1 ppm); followed **(*S*)-2-(benzylamino)-2-oxo-1-((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl but-2-ynoate (3.29)** (6 mg, 0.015 mmol, 30%) as white solid; M.p. = 147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44- 7.28 (5H, m, H- 22-26), 6.51 (1H, s, NH), 5.27 (1H, s, H-7), 5.16 -4.62 (4H, m, H-1, 2, 4, 5), 4.51 (2H, dd, *J* = 30.1, 5.8 Hz, H-16), 2.66 (1H, m, H-3a), 2.00-2.09 (1H, m, H-3b), 1.59 (3H, s, H-28), 1.43 (3H, t, *J* = 1.6 Hz, H-12); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3 (C-14), 151.5 (C-18), 137.1 (C-17), 128.9 (C-23, 25), 127.9 (C-24), 127.7 (C-22, 26), 89.1 (dd, *J* = 189.1, 15.0 Hz, C-1). 88.5 (dd, *J* = 189.5, 16.7 Hz, C-5), 85.9 (dd, *J*= 186.6, 8.5 Hz, C-2, 4), 74.1 (C-27), 71.0 (C-19), 60.4 (C-7), 43.5 (C-16), 28.2 (C-3), 23.8 (C-6), 12.4 (C-12), 4.1 (C-28); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -194.5 (d, *J* = 7.3 Hz, F-2, 4), -194.5 (d, *J* = 7.3 Hz, F-1, 5); IR : ν max/cm^{-1} 3550 (N-H), 1680, 1653 (C=O), 1558 (C-C); FTMS (ESI^{+}) *m/z* calcd for ([M]+H) 400.1535; found 400.1517 (Δ 4.5 ppm);



(*S*)-*N*-benzyl-2-(*N*-(4-methoxyphenyl)acetamido)-2-((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)acetamide (3.30) and (*S*)-2-(benzylamino)-2-oxo-1-((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl acetate (3.31)

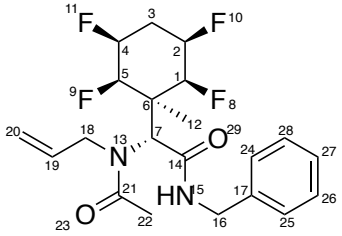


Following general procedure A using 0.05 mmol. of tetrafluoro aldehyde **3.10.a** with an appropriate components (*p*-anisidine, benzyl isocyanide and actic acid). The crude product was purified by means of column chromatography (petroleum ether/ EtOAc 8:2) to furnish **3.30** (6 mg, 0.0125 mmol, 25%) as orange solid; M.p. = 47 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43- 7.30 (5H, m, H- 22-25), 7.02- 6.93 (4H, m , H-27, 28, 30, 31), 5.27 - 4.78 (5H, m, H-1, 2, 4, 5, 7), 4.48 (2H, d, *J* = 5.8 Hz, H-16), 3.84 (1H, m , H-3a), 2.62 (1H, s, H-3b), 1.87 (3H, s, H-19), 1.37 (1H, s, H-12); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6 (C-18), 168.5 (C-14), 159.6 (C-29), 137.6 (C-17), 135.7 (C-32) 128.9 (C-22, 26), 128.0 (C-23, 25), 127.8 (C-24), 114.8 (C-28, 30), 114.5 (C-27, 31), 87.4-84.8 (m, C-1, 2, 4, 5), 56.6 (C-7), 55.4 (C-34), 46.5 (C-6), 126.1 (C-32), 43.8 (C-16), 27.7 (C-3) 24.1 (C-19), 13.2 (C-12); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -193.9 (2F, AA'XX'), -194.1 (2F, s br); IR: ν max/cm^{-1} 3332 (N-H), 2924 (C-H), 1745, 1662 (C=O), 1529(C-C); FTMS (ESI^{+}) *m/z* calcd for ([M]+Na) 503.1933; found 503.1925 (Δ 1.6 ppm); followed by **(*S*)-2-(benzylamino)-2-oxo-1-((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl acetate (3.31)** (7 mg, 0.018 mmol, 37%) as orange oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.30 (5H, m, H- 22-26), 6.43 (1H, s br, NH), 5.23 (1H, s, H-7), 5.15-4.64 (4H, m, H-1, 2, 4, 5), 4.54 (1H, dd, *J* = 14.8, 5.9 Hz, H-16a), 4.46 (1H, dd, *J* = 14.7, 5.8 Hz, H-16b), 2.74-2.57 (1H, m, H-3a), 2.22 (3H, s, H-19), 2.17-2.03 (1H, m, H-3b), 1.40 (3H, *J* = 1.6 Hz, H-12); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4 (C-14), 169.0 (C-18), 137.1 (C-17), 128.9 (C-22, 26), 128.0 (C-24), 127.7 (C-23, 25), 89.2 (d, *J* = 188.1, 26.0 Hz, C-1, 5), 86.9 (d, *J* = 174, 22.7 Hz, C-2, 4), 73.3 (C-7), 45.5 (C-6), 43.5 (C-16), 29.6 (C-3), 20.8 (C-19), 12.5 (C-12); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -194.5 (d, *J* = 7.5 Hz, F-2, 4), -194.6 (d, *J* = 7.4 Hz, F-1, 5); IR: ν_{max}/cm^{-1} 3337 (N-H), 2922, 2851 (C-H), 1747, 1668 (C=O); FTMS (ESI^{+}) *m/z* calcd for ([M]+Na) 398.1355; found 398.1345 (Δ 2.5 ppm);



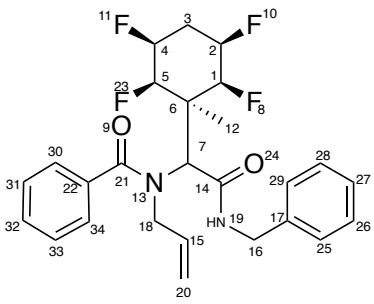
Following general procedure B using 0.025 mmol. of tetrafluoro aldehyde **3.10.a** with an appropriate components **A2, B1** and **C1** after the purification furnished compound **3.30** only (5 mg, 0.013 mmol, 53%).

2-(*N*-Allylacetamido)-*N*-benzyl-2,3,5,6-tetrafluoro-1-methylcyclohexyl)acetamide (3.32)



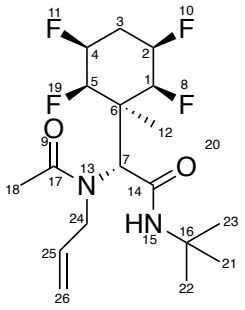
Following general procedure A using 0.05 mmol. of tetrafluoro aldehyde **3.10.b** with an appropriate components (allylamine, benzyl isocyanide and acetic acid) after the purification using column chromatography (petroleum ether/ EtOAc 6: 4) furnished compound **3.32** (15 mg, 0.036 mmol, 72%) as white solid; M.p.= 138-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40- 7.27 (5H, m, H- 24-28), 6.83 (1H, s br, NH), 5.86-5.69 (1H, m, H-19), 5.23 (2H, d, *J* = 10.8 Hz, H-20), 5.17- 4.53 (5H, H-1,2,4,5,7), 4.48 (2H, dd, *J* = 14.8, 5.9 Hz, H-16a), 4.35 (1H, dd, *J* = 14.7, 5.9 Hz, 2H), 4.30 (1H, d, *J* = 17.6 Hz, H-18a), 4.08-3.98 (1H, m, H-18b), 2.74-2.57 (1H, m, 3a), 2.48 - 2.35 (1H, m, H-3b), 2.22 (3H, s, H-22), 1.25 (3H, s, H-12); ^{13} (101 MHz, $CDCl_3$): δ 173.2 (C-21), 168.3 (C-14), 137.6 (C-17), 133.2 (C-20), 128.7(C-24, 25) , 127.7 (C-26, 28), 127.6 (C-27), 110.0 (C-19), 90.1 (dd, *J* = 189.0 Hz, 21.8, C-3, 4), 85.5 (dd, *J* = 182.4, 47.9 Hz, C-1, 5), 67.0 (C-7), 45.9 (C-18), 45.1 (C-6), 43.6 (C-16), 27.3 (C-3), 22.9 (C-22), 15.3 (C-12); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -194.5 (s br, F-2), -195.6 (s br, F-4), -202.1 (dd, *J* = 26.9, 14.0 Hz, F-1), -206.3 (s br, F-5); IR : ν max/cm^{-1} 3203 (N-H), 1668 (C=O), 1627 (C=O), 1012 (C-N); FTMS (ESI^{+}) *m/z* calcd for ([M]+H) 415.2008; found 415.1988 (Δ 4.8 ppm);

***N*-allyl-*N*-((*R*)-2-(benzylamino)-2-oxo-1-((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl)benzamide (3.33)**

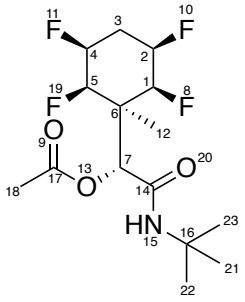


Following general procedure A using 0.063 mmol. of tetrafluoro aldehyde **3.10.b** with an appropriate components (allylamine, benzyl isocyanide and benzoic acid) after the purification using column chromatography (petroleum ether/ EtOAc 7:3) furnished compound **3.33** (24 mg, 0.050 mmol, 80%) as white solid; M.p. = 196-197 °C**;** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56- 7.30 (10H, m, H- 25-34), 5.65- 5.57 (1H, m, H-15), 4.6-4,42 (7H, m, H-1, 2, 4, 5, 7, 20), 4.54 (1H, dd, *J* = 14.8, 5.8 Hz, H-16a), 4.46 (1H, dd, *J* = 14.8, 5.6 Hz, H-16b), 4.29 (1H, dd, *J* = 15.6, 5.2 Hz, H-18a), 4.05-3.34 (1H, m, H-18b), 2.78- 2.59 (1H, m, H-3a), 2.52- 2.40 (1H, m, H-3b), 1.33 (3 H, s, H-12); ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.9 (C-21), 172.9 (C-14), 135.7 (C-17), 130.6 (C-22), 128.8 (C-26, 28, 31, 33), 127.8 (C-27, 32), 127.6 (C-19) 126.8 (C-25, 29, 30, 34), 110.0 (C-20), 90.1 (d, *J* = 180.3 Hz, C-2, 4), 85.7 (d, *J* = 167.1 Hz, C-1, 5), 61.0 (C-7), 45.4 (C-6), 43.6 (C-16), 27.3 (C-3), 16.1 (C-12); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -194.3 (dd, *J* = 13.6, 4.4 Hz, F-2), -195.3 (s br, F-4) , -202.1 (s br, F-3) , -205.7 (s br, F-5); IR : ν max/cm^{-1} 3259 (N-H), 1734 (C=O), 1668 (C=O), 1012 (C-N); FTMS (ESI^{+}) *m/z* calcd for ([M]+H) 477.2165; found 477.2146 (Δ 3.9 ppm);

(*R*)-2-(*N*-allylacetamido)-*N*-(*tert*-butyl)-2-((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)acetamide (3.34) and 2-(*tert*-Butylamino)-2-oxo-2,3,5,6-tetrafluoro-1-methylcyclohexyl) (3.35)



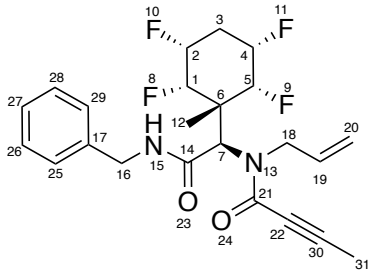
Following general procedure A using 0.05 mmol. of tetrafluoro aldehyde **3.10.b** with an appropriate components (allylamine, *tert*-butyl isocyanide and acetic acid) after the purification using column chromatography (petroleum ether/ EtOAc 8:2) furnished **3.34** (5 mg, 0.013 mmol, 26%) as a white solid; M.p. = 146-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (1H, s, NH), 5.83 (1H, s, H-15), 5.35-5.21 (3H, m, H-19, H-7), 5.20-4.50 (4H, m, H-1, 2, 4, 5), 4.40 (1H, d, *J* = 17.3 Hz, H-17a), 4.04 (1H, dd, *J* = 17.4, 6.0 Hz, H-17b), 2.77-2.53 (1H, m, H-3a), 2.41 (1H, m, H-3b), 2.23 (3H, s, H-21), 1.35 (9H, s, H-24, 25, 26), 1.23 (3H, t, *J* = 1.3 Hz, H-12); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.6 (C-17), 167.8 (C-14), 133.6 (C-25), 117.9 (C-26), 90.2 (dd, *J* = 190.7, 21.0 Hz, C-1, 5), 85.6 (dd, *J* = 178.5, 21.5 Hz, C-2, 4), 62.1 (C-7), 51.7 (C-16), 45.8 (C-6), 32.0 (C-17), 28.5 (C-24, 25, 26), 27.3 (C-3), 22.9 (C-21), 14.2 (C-12); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -194.41 (d, *J* = 4.4 Hz, F-2), -195.3 (s br, F-4) , -202.1 (s br, F-1), -206.3 (s br, F-5); IR : ν max/cm^{-1} 3367 (N-H), 3240 (C-H), 1749 (C=O), 1654 (C=O); FTMS (ESI+) m/z calcd for([M]+Na) 403.1985; found 403.1971 (Δ 3.5 ppm); followed by **3.35:** (6 mg, 0.021 mmol, 41%) as a white solid; M.p. = 161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (1H, s, NH), 5.28 (1H, d, *J* = 1.1 Hz, H-7), 4.96- 4.61 (4H, m, H-1,2,4,5), 2.76-2.58 (1H, m, H-3a), 2.45 (1H, dt, *J* = 10.8, 5.1 Hz, H-3b), 2.20 (3H, s, H-18), 1.40 (9H, s, H-21, 22, 23), 1.07 (3H, s, H-12); ^{13}C NMR (101 MHz $CDCl_3$): δ 169.7 (C-16), 165.5 (C-14), 90.2 (dd, *J* = 173.1, 21.0 Hz, C-1), 88.3 (dd, *J* = 182.0, 21.3 Hz, C-2), 86.5-84.1 (m, C-4, 5), 71.2 (C-7), 52.0 (C-20), 43.8 (C-6) 28.6 (C-21, 22, 23), 27.6 (C-3), 20.6 (C-17), 13.5 (C-12); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -195.2 (dd, *J* = 13.9, 4.4 Hz), -195.4 (dd, *J* = 12.8, 4.5 Hz), -204.2 (dd, *J* = 22.0, 12.3 Hz), -207.6 (dd, *J* = 22.1, 13.9 Hz); IR : ν max/cm^{-1} 3408 (N-H), 2976, 2932 (C-H), 1746 (C=O), 1668 (C=O); FTMS (ESI^{+}) *m/z* calcd for ([M]+Na^{+}) 364.1511; found 364.1496 (Δ 4.1 ppm);



***N*-allyl-*N*-((*R*)-2-(*tert*-butylamino)-2-oxo-1-((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl)benzamide (3.36) and (*R*)-2-(*tert*-butylamino)-2-oxo-1-((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl benzoate (3.37)**

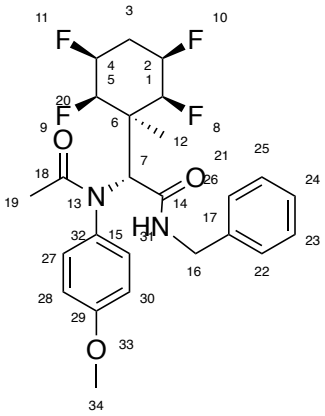
Following general procedure A using 0.05 mmol. of tetrafluoro aldehyde **3.10.b** with an appropriate components (allylamine, *tert*-butyl isocyanide and benzoic acid). The crude product was purified by means of column chromatography (petroleum ether/ EtOAc 6:4) to offer **3.36** (4 mg, 0.0091 mmol, 18%) as a white solid; M.p. = 194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.35 (5H, m, H- 21-25), 7.02 (1H, s br), NH), 5.73 (1H, m, H-30), 5.18 (3H, m, H-7, H-31), 4.85 (4H, m, H-1, 2, 4, 5), 4.33 (1H, dd, *J* = 15.7, 4.9 Hz, H-29a), 4.00 (1H, m, H- 29b), 2.66 (1H, m, H-3a), 2.44 (1H, m, H-3b), 1.40 (9H, s, H-26, 27, 28), 1.34 (3H, s, H-12); ^{13}C NMR (126 MHz, $CDCl_3$): δ 183.8 (C-14), 174.7 (C-17), 136.0 (C-18), 132.6 (C-30), 130.5 (C-23), 128.7 (C-22, 24), 126.7 (C-21, 25), 119.8 (C-31), 90.2 (dd, *J*= 189.3, 21.8 Hz, C-2,4), 85.5 (d, *J* = 183.5, 46.0 Hz, C-1,5), 73.5 (C-7) 51.7 (C-16), 45.9 (C-6), 29.7 (C-29), 28.6 (C- (26-28)), 27.3 (C-3), 16.0 (C-12); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -194.3 (dd, *J* = 13.5, 4.2 Hz), -195.2 (s br) , -202.4 (s br) , -205.6 (s br); IR : ν max/cm^{-1} 3309 (N-H), 2902, 2850 (C-H), 1434 (C=O), 167 2 (C=O), 1631 (C=C); FTMS (ESI^{+}) *m/z* calcd for([M]+Na^{+}) 465.2141; found 465.2125 (Δ 3.4 ppm); followed by **(*R*)-2-(*tert*-butylamino)-2-oxo-1-((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl benzoate (3.37)** (5 mg, 0.012 mmol, 25%) as a white solid; M.p.= 214-215 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16-8.00 (2H, m, H-21, 25), 7.71-7.58 (1H, m, H-23), 7.56-7.44 (1H, m, H-22, 24), 5.99 (1H, s, NH), 5.58 (1H, d, *J* = 1.1 Hz, H-7), 5.09-4.61 (4H, m, 1, 2, 4, 5), 2.85 -2.63 (1H, m, H-3a), 2.47 (1H, m, H-3b), 1.41 (9H, s, H- 26-28), 1.23 (3H, t, *J* = 1.3 Hz, H-12); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.2 (C-14), 165.1 (C-17), 133.8 (C-23), 130.4 (C-18), 129.8 (C-21, 25), 128.6 (C-22, 24), 90.4 (d, *J* = 167.9, 19.7 Hz, C-1, 5), 85.4 (dd, *J* = 182.6, 21.9 Hz, C-2,-4), 71.4 (C-7), 51.7 (C-16), 44.6 (C-6), 28.6 (C-26, 27, 28), 27.3 (C-3), 13.7 (C-12); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -195.1 (dd, *J* = 13.9, 4.6 Hz), -195.4 (dd, *J* = 12.7, 4.4 Hz), -204.3 (dd, *J* = 22.4, 12.5 Hz), -207.0 (dd, *J* = 22.4, 14.1 Hz); IR : ν max/cm^{-1} 3424 (N-H), 2915, 2851 (C-H), 1718 (C=O), 1684 (C=O); FTMS (ESI^{+}) *m/z* calcd for([M]+Na) 426.1668; found 426.1652 (Δ 3.8 ppm);

N-allyl-N-((R)-2-(benzylamino)-2-oxo-1-((1r,2R,3S,5R,6S)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl)but-2-ynamide (3.38)



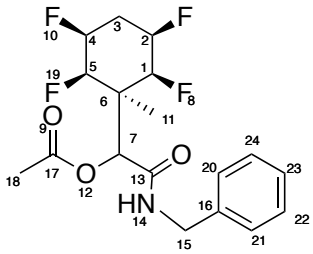
Following general procedure A using 0.05 mmol. of tetrafluoro aldehyde **3.10.b** with an appropriate components (allylamine, benzyl isocyanide and 2-butynoic acid). The crude product was purified by means of column chromatography (petroleum ether/ EtOAc 6:4) to offer **3.38** (10 mg, 0.22 mmol, 46%) as a white solid; M.p. = 161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42- 7.27 (5H, m, H- 25-29), 6.69 (1H, s, NH), 5.91-5.78 (1H, m, H-19), 5.43-5.08 (3H, m, H-7, 20), 5.06- 4.54 (4H, m, H-1, 2, 4, 5), 4.49 (1H, dd, *J* = 14.8, 5.8 Hz, H-16a), (dd, *J* = 14.9, 5.5 Hz, H-16b), 4.30-3.97 (2H, m, H-18), 2.73-2.56 (1H, m, H-3a), 2.41 (dt, *J* = 10.8, 5.2 Hz, H-3b), 2.06 (3H, s, H-31), 1.24 (3H, s, H-12); ^{13}C NMR (101 MHz $CDCl_3$): δ 167.8 (C-14), 156.8 (C-21), 137.6 (C-17), 132.8 (C-19), 128.7 (C-26, 28), 127.7 (C-27), 127.5 (C-25, 29), 117.8 (C-20), 91.9 (C-30), 90.0 (d, *J* = 188.9, 20.3 Hz, C- 1, 5), 85.5 (d, *J* = 184.1,34.5 Hz C-2, 4), 73.5 (C-22), 61.8 (C-7), 48.0 (C-18), 43.6 (C-16), 29.2 (C-6), 27.3 (C-3), 15.6 (C-12), 4.18 (C-31); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -194.4 (d, *J* = 13.9, Hz), -195.4 (d, *J* = 11.5, Hz), -201.5 (s br), -206.7 (dd, *J*= 25.7, 12.8, Hz); IR : ν max/cm^{-1} 3350 (N-H), 2914, 2850 (C-H), 2239 (C≡C) 1735 (C=O), 1627 (C=C); FTMS (ESI^{+}) *m/z* calcd for ([M]+Na^{+}) 461.1828; found 461.1814 (Δ 3.7 ppm);

(R)-N-benzyl-2-(N-(4-methoxyphenyl)acetamido)-2-((1r,2R,3S,5R,6S)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)acetamide (3.39)



Following general procedure B using 0.05 mmol. of tetrafluoro aldehyde **3.10.a** with an appropriate components (*p*-anisidine, benzyl isocyanide and actic acid) after the purification by means of column chromatography (petroleum ether/ EtOAc 8:2) resulted in compound **3.39** (11 mg, 0.0229 mmol, 46%) as white solid; M.p. = 167 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39- 7.29 (5H, m, H- 22-26), 6.89-6.78 (4H, m, H-27, 28, 30, 31), 6.25 (1H, s br, NH), 5.18-4.60 (4H, m, H-1, 2, 4, 5), 4.49 (1H, dd, *J* = 14.0, 6.4, H-16a), 4.45-4.33 (2H, m, H-7, 16b), 3.78 (3H, s, H-34), 2.76-2.62 (1H, m H-3a), 2.53- 2.38 (1H, m, H-3b), 1.28 (3H, s, H-19), 1.02 (3H, s, H-12); ^{13}C NMR (101 MHz $CDCl_3$): δ 174.5 (C-18), 170.3 (C-14), 154.1 (C-29), 141.3 (C-32), 137.3 (C-17), 128.8 (C-22, 26), 127.7 (C-24), 127.6 (C-23, 25), 118.5 (C-27, 31), 114.8 (C-28, 30), 90.8 (dd, *J* = 185.5, 20.0 Hz C-1, 5), 85.6 (dd, *J* = 185.1,27.9 Hz, C-2, 4), 60.5 (C-7), 55.7 (C-34), 43.8 (C-16), 43.3 (C-6), 29.7 (C-19), 27.3 (C-3), 13.0 (C-12); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -194.7 (dd, *J* = 14.9, 4.2 Hz), -195.4 (dd, *J* = 12.6, 4.2 Hz), -203.8 (dd, *J* = 24.2, 12.5 Hz), -205.0 (dd, *J* = 24.1, 14.8 Hz); IR: ν max/cm^{-1} 3296(N-H), 2922 (C-H), 1647 (C=O); FTMS (ESI^{+}) *m/z* calcd for ([M]+Na) 503.1933; found 503.1916 (Δ 3.4 ppm);

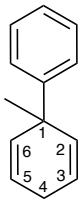
(*R*)-2-(benzylamino)-2-oxo-1-((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl acetate (3.40)



Following general procedure A using 0.05 mmol. of tetrafluoro aldehyde **3.10.b** with an appropriate components (*p*-anisidine, benzyl isocyanide and acetic acid) after the purification resulted in compounds **3.39** (traces of compound are detected on ^{19}F NMR of crude material) and **(*R*)-2-(benzylamino)-2-oxo-1-((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)ethyl acetate (3.40)** (8 mg, 0.021 mmol, 43%) as yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.29 (5H, m, H- 20-24), 6.89-4.61 (5H, m, H-1,2,4,5,7), 4.58 (1H, dd, *J* = 14.6, 6.1 Hz, H-15a), 4.51 (1H, dd, *J* = 14.5, 5.9 Hz, H-15b), 2.80-2.53 (1H, m, H-3a), 2.50- 2.34 (1H, m, H-3b), 1.90 (3H, s, H-18), 0.73 (3H, t, *J* = 1.3 Hz, H-12); ^{13}C NMR (126 MHz $CDCl_3$): δ 171.5 (C-13), 170.4 (C-17), 137.5 (C-16), 128.9 (C- 21, 25), 127.9 (C-23), 127.8 (C-22, 24), 89.7 (dd, *J* = 182.6, 27.5 Hz, C-1, 5), 85.7 (dd, *J* = 171.9, 27.0 Hz, C-2, 4), 68.9 (C-7), 43.6 (C-15), 31.9 (C-6), 29.7 (C-18), 27.5 (C-3), 12.5 (C-11); ^{19}F observe with ^{1}H decoupling NMR (376 MHz, $CDCl_3$): δ -194.7 (dd, *J* = 14.0, 4.1 Hz), -195.2 (dd, *J* = 13.0, 4.0 Hz), -205.6 (dd, *J* = 22.1, 13.0 Hz), -208.2 (dd, *J* = 22.1, 13.8 Hz); IR: ν max/cm^{-1} 3265 (N-H), 2922 (C-H), 1700, 1683 (C=O), 1018 (C-O); FTMS (ESI^+) *m/z* calcd for ([M]+Na) 398.1355; found 398.1343 (Δ 3.0 ppm);

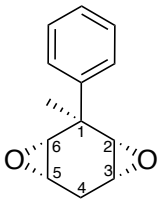
7.2.3. Chapter 4.

(1-methyl-2,5-cyclohexadien-1-yl)-Benzene (4.11)



To biphenyl (30 g, 192 mmol), ammonia (400 mL) was added at the -78 °C. Lithium (3.065 g, 441 mmol) was then added in small portions at - 78 °C until slowly dark blue colour persisted. After 2 h stirring, iodomethane (48 mL, 770 mmol) was added slowly over a period of 5 min, during which the color gradually changed to yellow and ended up as pale yellow. Ammonia was evaporated, water (400 mL) was slowly added and extracted with diethyl ether (200 mL x 3). The combined organic phases were washed with sodium sulfite (200 mL x 2) and water (300 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure, resulting in 1-methyl-1,4-dihydro-1,1'-biphenyl **4.11** (32.6 g, 191 mmol, 99%) as colourless oil. No further purification was required; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.42 (2H, m, Ar), 7.41-7.22 (3H, m, Ar), 5.86-5.80 (2H, m, H-3, 5), 5.74 (2H, dt, J = 10.4, 2.0 Hz, H-2, 6), 2.78 (2H, ddd, J = 5.0, 2.8, 1.2 Hz, H-4), 1.56 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.5 (Ar), 134.4 (Ar), 128.2 (Ar), 126.6 (C-2, 6), 125.9 (Ar), 121.8 (C-3, 5), 40.2 (C-1), 28.0 (C-4), 25.9 (CH_3); FTMS (ESI^-) *m/z* calcd for ([M]-H) 169.1017; found 169.1009 (Δ 3.7 ppm);

(1*R*,2*s*,3*S*,5*R*,7*S*)-2-methyl-2-phenyl-4,8-dioxatricyclo octane (4.12)



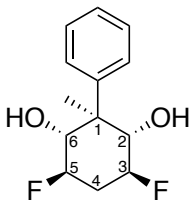
*m*CPBA (99.58 g, 577 mmol) was added to a solution of diene **4.11** (32.5 g, 190 mmol) in CH_2Cl_2 (200 mL) at 0 °C. The reaction was allowed to warm gradually to rt and stirred for 48 h. The white precipitate formed was filtered and the filtrate was washed with 10% aq. KOH, (100 mL). The aqueous layer was then extracted with DCM (100 mL x 3). The combined organic layers were washed with distilled water (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Resulting in yellow oil (46 g) was purified by silica gel column chromatography (petroleum ether/ Et.Ac. 9:1), to give **4.12** as white crystalline solid (26.1 g, 129 mmol, 68%); M.p.= 86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.32 (5H, m, Ar), 3.31 (2H, ddd, J = 4.1, 2.8, 1.3 Hz, H-2, 6), 3.00-2.96 (2H, m, H-3, 5), 2.95-2.87 (1H, m, H-4a), 2.42 (1H, dt, J = 17.3, 2.9 Hz, H-4b), 1.81 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 142.2 (Ar), 129.0 (Ar), 127.6 (Ar), 126.6 (Ar), 58.2 (C-2, 6), 51.4 (C-3, 5), 38.3 (C-1), 23.3 (C-4), 19.8 (CH_3); IR: ν_{max}/cm^{-1} 2987 (C-H), 1267 (C-O-C); FTMS (ESI^+) *m/z* calcd for ([M]+Na) 225.08915; found 225.088 (Δ 3.7 ppm);

Difluoro-methyl-phenylcyclohexane-diols (4.13 and 4.14)

In a dry Teflon flask, $Et_3N.3HF$ (6.5 mL, 39.6 mmol) was added to diepoxide **4.12** (1g, 4.96 mmol) at room temperature. After stirring the mixture at 135 °C for 48 h, the mixture was cooled down to room temperature, 10% aq. $NaHCO_3$ (200 mL) was added and extracted with Et.Ac**.** (15 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The yellow oily residue was then passed through silica gel pad (petroleum ether/DCM 1:1) to yield quantitative amount of crude product of 1.22 g, which has been taken to the next stage without purification.

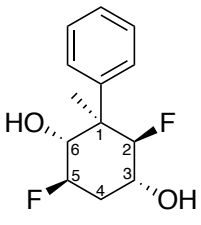
Analytical sample has been purified with silica gel chromatography (petroleum ether: diethyl ether / 8:2) to yield pure product **4.13** as yellow solid and **4.14**.

(1*R*,2*s*,3*S*,4*S*,6*R*)-4,6-difluoro-2-methyl-2-phenylcyclohexane-1,3-diol (4.13)



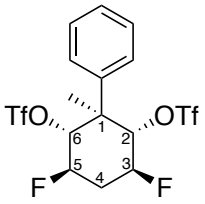
M.p. = 128-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.38 (5H, m, Ar), 4.74 (2H, ddd, *J* = 49.1, 11.7, 8.9 Hz, H-3, 5), 4.04 (2H, dd, *J* = 13.2, 9.1 Hz, H-2, 6), 2.78 (1H, dd, *J* = 11.7, 6.3 Hz, H-4a), 2.00 (1H, m, H-4b), 1.36 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1 (Ar), 129.0 (Ar), 127.4 (Ar), 126.4 (Ar), 90.2 (dd, *J* = 175.3, 15.8 Hz, C-3, 5), 77.3 (dd, *J* = 19.71, 2.58 Hz, C-2, 6), 47.6 (C-1), 33.2 (t, *J* = 20.7 Hz, C-4), 11.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -188.7 (dt, *J* = 50.3, 12.6 Hz, F-3, 5); ^{19}F [^{1}H] NMR (376 MHz, $CDCl_3$): δ -188.7 (F-3, 5); IR: ν_{max}/cm^{-1} 3581, 3435 (O-H), 2962 (C-H), 1498 (C-C), 1267 (C-O), 1083, 1031 (C-F); TOF MS (EI$^+$) *m/z* calcd for ([M])$^+$ 242.1118; found 242.1120 (Δ 3.7 ppm);

(1*R*,2*R*,3*R*,4*R*,6*R*)-3,6-difluoro-2-methyl-2-phenylcyclohexane-1,4-diol (4.14)



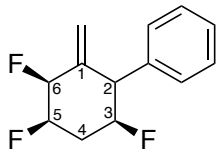
^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.58-7.36 (5H, m, Ar), 5.08 (1H, dddd, *J* = 50.9, 11.1, 8.6, 4.9 Hz, H-5), 4.69-4.51 (2H, m, 2H, H-2, H-6), 4.41 (1H, dt, *J* = 8.0, 3.7 Hz, H-3), 2.36 (1H, m, H-4a), 2.19 (1H, m, H-4b), 1.56 (3H, d, *J* = 1.8 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) *δ:* 144.0 (Ar), 128.4 (Ar), 126.7 (Ar), 126.7 (Ar), 96.5 (d, *J* = 178.3 Hz, C-2), 91.1 (d, *J* = 169.4 Hz, C-5), 72.9 (d, *J* = 18.2 Hz, C-6), 68.9 (dd, *J* = 32.4, 13.1 Hz, C-3), 33.5 (d, *J* = 18.9 Hz, C-4), 18.5 (d, *J* = 6.0 Hz, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) *δ* -183.6 (dm, *J* = 43.6 Hz, F-2), -194.4 (dd, *J* = 50.8, 10.5 Hz, F-3); ^{19}F [^{1}H] NMR (376 MHz, $CDCl_3$) *δ:* -183.6 (s, F-2), -194.4 (F-3); IR: ν_{max}/cm^{-1} 3574, 3471 (O-H), 2924 (C-H), 1498, 1417 (C-C), 1247 (C-O), 1205 (C-F); FTMS (ESI$^+$) *m/z* calcd for([M]+Na) 265.1016; found 265.1009 (Δ 3.7 ppm);

(1*R*,2*s*,3*S*,4*S*,6*R*)-4,6-difluoro-2-methyl-2-phenylcyclohexane-1,3-diyl bis(trifluoromethanesulfonate) (4.15)

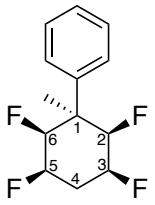


Trifluoromethanesulfonic anhydride (3.4 mL, 20.13 mmol) was slowly added at 0°C to a mixture of **4.13** and **4.14** (1.22 g) in pyridine (10 mL),. After 18 h stirring at rt, the reaction mixture was quenched with a mixture of water (50 mL) and copper sulphate (2 mL) and extracted with diethyl ether (50 mL x3). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Dark orange solid was re-dissolved in minimum amount of DCM and filtered through silica, resulting in pure 2 g of triflated crude material, which was taken straight to fluorination stage. Analytical sample was purified by means of column chromatograph (petroleum ether: DCM/ 9:1), resulting in pure compound **4.15**; M.p. = 139 °C (decomposed, turned black); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.59-7.36 (5H, m, Ar), 5.23 (2H, dd, *J* = 11.7, 9.1 Hz, H-2,6), 5.12-4.87 (2H, m, H-3, 5), 3.11-2.96 (1H, m, H-4a), 2.29-2.12 (1H, m, H-4b), 1.58 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) *δ:* 135.9 (Ar), 129.4 (Ar), 129.2 (Ar), 126.5 (Ar), 117.9 (q, *J* = 320.2 Hz , CF_3), 89.1 (d, *J* = 17.6 Hz, C-2, 6), 85.8 (dd, *J* = 185.3, 15.1 Hz, C-3, 5), 47.1 (C-1) , 31.9 (t, *J* = 21.7 Hz, C-4), 12.9 (CH_3); ^{19}F [^{1}H] NMR (376 MHz, $CDCl_3$) *δ:* -74.6 (d, *J* = 8.3 Hz, CF_3), -187.8 (q, *J* = 7.5 Hz, F-3); IR: ν_{max}/cm^{-1} 1411, 1400 (S=O), 1205 (C-O), 918 (S-O); FTMS (nESI^{+}) *m/z* calcd for ([M]+H) 507.0177; found 507.3282 (Δ 3.7 ppm);

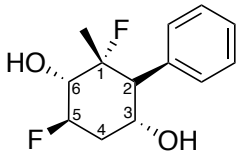
((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)benzene (4.16) and ((1*R*,3*S*,4*R*,6*S*)-3,4,6-trifluoro-2-methylenecyclohexyl)benzene (4.18)



$Et_3N.3HF$ (6.1 mL, 38 mmol) was added to compound **4.15** (2 g, 3.95 mmol) at rt. After 48 h stirring at 115 °C, the mixture was cooled down to rt, poured into 10% of aq. $NaHCO_3$ (30 mL) and extracted with diethyl ether (50 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product (1.296 g) was purified using column chromatography (petroleum ether: DCM/ 7:3) furnishing **4.18** as a white crystalline solid (0.213 g, 0.87 mmol, 17%): M.p.= 109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.30 (5H, m, Ar), 5.53 (1H, tt, *J* = 1.7, 0.8 Hz, $=CH_{2\text{-}a}$), 5.34-4.92 (2H, m, H-3, 5), 4.90-4.83 (1H, m, $=CH_{2\text{-}b}$), 3.45 (1H, d, *J* = 37.6 Hz, H-6), 2.84-2.67 (1H, m, H-4a), 2.19-1.89 (1H, m, H-4b), 1.60-1.47 (1H, m, H-2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.3 (d, *J* = 14.9 Hz, C-2), 130.6 (d, *J* = 5.1 Hz, Ar), 130.0 (d, *J* = 4.4 Hz, Ar), 128.5 (Ar), 127.6 (Ar), 113.5 (d, *J* = 10.1 Hz, $=CH_{2\text{-}a}$), 90.7 (dd, *J* = 194.4, 18.9, C-6), 89.7 (d, *J* = 189 Hz, C-3), 88.1 (dd, *J* = 184.9, 20.1 Hz, C-5), 51.9 (dd, *J* = 19.6, 2.7 Hz, C-2), 33.7 (td, *J* = 20.2, 6.2 Hz, C-4); ^{19}F NMR (377 MHz, $CDCl_3$): δ -185.4-(-186.4) (m, F-3), -194.5 (ddq, *J* = 45.0, 12.6, 6.3 Hz, F-6), -197.7-(-199.6) (m, F-5); ^{19}F NMR (decoupled) (377 MHz, $CDCl_3$): δ -186.0 (d, *J* = 20.2 Hz, F-3), -194.6 (d, *J* = 12.9 Hz, F-6), -198.64 (dd, *J* = 19.9, 12.8 Hz, F-5); IR: ν_{max}/cm^{-1} 1111, 1056 (C-F); FTMS (APCI$^+$) *m/z* calcd for ([M]) 226.0919*;* found 226.0914; calcd for ([M]-H) 225.0886*;* found 225.0884 (Δ 3.7 ppm); followed by **((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)benzene (4.16)** (0.307 g, 1.34 mmol, 25%)*:* M.p.= 143 °C (decomposed, changed colour from white to yellow); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.39 (5H, m, Ar), 5.47-5.21 (2H, dd*, J* = 47.5, 8.9 Hz, H-2, 6), 5.13-4.88 (2H, m, H-3, 5), 2.79 (1H, m, H-4a), 2.53 (1H, m, H-4b); ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.8 (Ar), 129.0 (Ar), 127.3 (Ar), 125.6 (Ar), 90.8 (dd, *J* = 193.1, 15.2 Hz, C-2, 6), 86.0 (dd, 198.7, 18.23, C-3, 5), 53.6 (C-1), 27.5 (C-4), 24.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -194.6 (d, *J* = 47.7 Hz, F-2, 6), -202.1 (m, F-3, 5); ^{19}F [^{1}H] NMR (376 MHz, $CDCl_3$): δ -194.6 (dd, *J* = 8.9, 5.6 Hz, F-2), -202.1 (dd, *J* = 8.8, 5.6 Hz, F-3); IR: ν_{max}/cm^{-1} 1502 (C-C), 1392 (C-F); FTMS (ESI$^+$) *m/z* calcd. for ([M]+Na)$^+$ 269.0929*;* found 269.0919 (Δ 3.7 ppm);

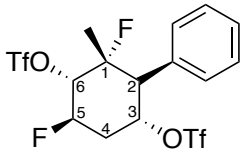


(1*S*,2*R*,3*R*,4*R*,6*R*)-2,6-difluoro-2-methyl-3-phenylcyclohexane-1,4-diol (4.20)



To a solution of diepoxide **4.12** (2 g, 9.84 mmol) in DCM (5 mL) was added Py.HF (0.982 mL, 1.96 mmol) at -78 °C. After 12 h stirring at rt, 10% of aq. $NaHCO_3$ (30 mL) was added, extracted with Et.Ac. (40 mL x 3). Combined organic layers were then washed with water (50 mL), and dried over $MgSO_4$, filtered and concentrated under reduced pressure. Dark orange solid was re-dissolved in minimum amount of DCM and filtered through silica (petroleum ether/ Et.Ac. 7:3), resulting in difluoro diol **4.20** as yellow crystalline solid (1.9 g, 7.85 mmol, 80%); M.p.= 146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.27 (5H, m, Ar), 5.02 (1H, ddt, *J* = 45.7, 6.0, 3.1 Hz, H-5), 4.37 (1H, td, *J* = 11.0, 4.6 Hz, H-3), 4.09 (1H, m, H-6), 3.42 (1H, dd, *J* = 13.3, 10.9 Hz, H-2), 2.45 (1H, m, H-4a), 2.12 (1H, m, H-4b), 1.27 (3H, dd, 25.3, 3.2Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.1 (Ar), 130.1 (Ar), 128.7 (Ar), 127.7 (Ar), 89.6 (dd, *J* = 169.5, 5.3 Hz, C-5), 72.7 (dd, *J* = 27.5, 19.2 Hz, C-6), 65.7 (d, *J* = 10.0 Hz, C-3), 53.9 (d, *J* = 18.8 Hz, C-2), 34.0 (d, *J* = 19.3 Hz, C-4), 20.0 (dd, *J* = 23.9, 7.2 Hz, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -143.8 (m, F-1), -186.9 (m, F-5); ^{19}F [^{1}H] NMR (376 MHz, $CDCl_3$): δ -143.8 (F-1), - 186.9 (F-5); IR: ν_{max}/cm^{-1} 3572 (O-H), 3468 (O-H), 2953 (C-H), 1498 (C-C), 1444 (C-C), 1072, 1008 (C-F); FTMS (ESI^{+}) *m/z* calcd for ([M]+Na^{+}) 265.252*;* found 265.1009 (Δ 3.7 ppm);

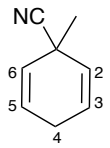
(1*S*,2*R*,3*R*,4*R*,6*R*)-2,6-difluoro-2-methyl-3-phenylcyclohexane-1,4-diyl bis(trifluoromethanesulfonate) (4.21)



Trifluoromethanesulfonic anhydride (5.6 mL, 33 mmol) was slowly added to a solution of difluoro diol **4.20** (1.9 g, 7.85 mmol) in pyridine (10 mL) and DCM (10 mL) at 0°C. The mixture was warmed to room temperature and left stirring for 3 h and then quenched with a mixture of water (50 mL) and aqueous copper sulphate (2 mL). The organics were then extracted with diethyl ether (50 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue (2.55 g) was re-dissolved in minimum amount of DCM and purified using column chromatography (petroleum ether/diethyl ether 95:5 to 9:1), to afford product **4.21** (0.78 g, 1.54 mmol, 19%) as yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.27 (5H, m, Ar), 5.44 (1H, td, *J* = 9.1, 4.5 Hz, H-3), 5.23-5.15 (2H, m, H-5, 6), 3.71 (1H, dd, *J* = 12.9, 9.2 Hz, H-2), 2.93-2.75 (1H, m, H-4a), 2.54 (1H, m, H-4b), 1.44 (3H, d, *J* = 23.8, 2.7 Hz, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 131.7 (d, *J* =2.2 Hz, Ar), 129.5 (Ar), 129.1 (Ar), 128.9 (Ar), 118.1 (q, *J* = 317 Hz, CF_3), 118.4 (q, *J* = 319 Hz, CF_3), 93.9 (d, *J* = 193 Hz, C-1), 86.0 (dd, *J* = 179.5, 5.2 Hz, C-5), 83.5 (dd, *J* = 26.3, 18.6 Hz, C-6), 82.3 (dd, *J* = 7.7, 3.1 Hz, C-3), 53.3 (d, *J* = 23.4 Hz, C-2), 33.0 (d, *J* = 20.5 Hz, C-4), 20.6 (dd, *J* = 23.9, 6.6 Hz, CH_3); ^{19}F NMR (470 MHz, $CDCl_3$): δ -73.9 (dd, *J* = 5.8, 3.5 Hz, 3F, C(6)-CF_3), -75.1 (s, 3F, C(3)-CF_3), -143.4 (s, 1F, F-1), -186.8 (s, 1F, F-5); IR: ν_{max}/cm^{-1} 1411, 1201 (S=O), 1138 (C-F), 891 (S-O); FTMS (ESI$^-$) *m/z* calcd for ([M-OTf])$^-$ 357.0584*;* found 357.0579 (Δ 3.7 ppm);

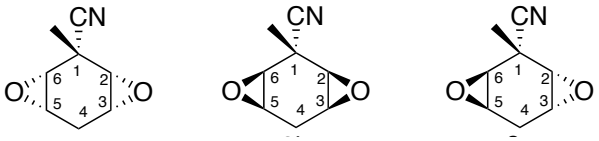
7.2.4. Chapter 5.

1-methylcyclohexa-2,5-diene-1-carbonitrile (5.2)



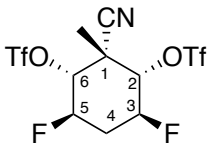
Following previously reported method, liquid ammonia was added to a three necked flask cooled to -78 °C, followed by an addition of lithium (2.40 g, 294 mmol) in small portions.[12] A solution of benzonitrile **5.1** (12 mL, 117.6 mmol) in THF (120 mL) and *tert*-butyl alcohol (11.2 mL, 117.6 mmol) was added dropwise to the reaction mixture. After 3 h of stirring at the following temperature, MeI (14.8 mL, 235 mmol) was added dropwise to the reaction. Ammonia was evaporated overnight followed by an addition of water (400 mL) and NH_4Cl (30 mg), the mixture was extracted three times with diethyl ether. The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduced pressure, resulting in **5.2**, 4.38 g, 37 mmol, 31% yield as colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89-5.94 (2H, m, H-3, 5), 5.70-5.65 (2H, m, H-2, 6), 2.78-2.60 (2H, m, H-4), 1.51 (3H, s, CH_3). [8,10,12]

(1*R*,2*r*,3*S*,5*R*,7*S*)-2-methyl-4,8-dioxatricyclo[5.1.0.03,5]octane-2-carbonitrile (5.3.a), (1*R*,2*s*,3*S*,5*R*,7*S*)-2-methyl-4,8-dioxatricyclo[5.1.0.03,5]octane-2-carbonitrile (5.3.b) and (1*S*,3*S*,5*R*,7*R*)-2-methyl-4,8-dioxatricyclo[5.1.0.03,5]octane-2-carbonitrile (5.3).c:



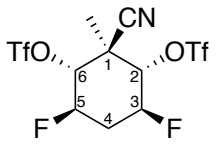
*m*CPBA (70%) (36 g, 148 mmol) was added to a solution compound **5.2** (3.6 g, 30 mmol) in DCM (400 mL) at rt. The reaction was allowed to warm to 35 °C and stirred for 24 h. The reaction mixture was then washed with aq. K_2CO_3 (10%) and the aqueous layer was then extracted with DCM (200 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give a colourless crystalline solid, with three diastereoisomers of diepoxide (**5.3.a, 5.3.b** and **5.3.c**) observed on ^{1}H NMR spectrum in a ratio of 10: 15: 13. Crude product was then purified by silica gel column chromatography (ethyl acetate/ petroleum ether = 9/ 1, 7.5/ 2.5) giving the desired compounds in two sets of fractions, compounds **5.3.b** and **5.3.c** as a mixture (Rf = 0.74 at ethyl acetate/ petroleum ether = 1/ 1) (1.59 g, 10.5 mmol, 35%); **5.3.b** (major): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.34-3.17 (4H, m, H-2, 3, 5, 6), 2.83 (1H, d, *J* = 17.5, H-4a), 2.51-2.31 (1H, m, H-4b), 1.67 (3H, s, CH_3); **5.3.c** (minor): ^{1}H NMR (400 MHz, CDCl3): δ 3.34-3.17 (2H, m, H-3, 5), 3.03-2.97 (2H, m, H-2, 6), 2.51-2.31 (1H, m, H-4a,b) 1.80 (3H, s, CH_3), followed by epoxide **5.3.a** (Rf = 0.15 at ethyl acetate/ petroleum ether = 1/ 1) (0.82 g, 5.4 mmol, 18%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.31- 3.20 (2H, m, H-3, -5), 3.16 (1 H, d, *J* = 3.7, H-1, 6), 2.87 (1H, d, *J* = 17.4, H-4a), 2.27 (1H, dt, *J* = 17.4, 2.9, H-4b), 1.65 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): 119.8 (CN), 54.1 (C-2, 6), 50.1 (C-3, 5), 33.4(C-1), 22.2 (C-4), 20.7 (CH_3).

(1*R*,2*r*,3*S*,4*S*,6*R*)-2-cyano-4,6-difluoro-2-methylcyclohexane-1,3-diyl bis(trifluoromethanesulfonate) 5.5.a

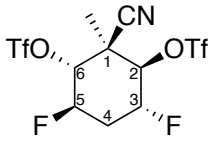


In a dry Teflon flask, $Et_3N.3HF$ (6.8 mL, 42.4 mmol) was added to diepoxide **5.3.a** (0.8 g, 5.3 mmol) at rt. After 12 h of stirring at 140 °C, the mixture was cooled to rt, poured into $NaHCO_3$ (100 mL) and extracted with dichloromethane (100 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure resulting in 0.71 g of yellow solid which was taken as a crude to the next stage, **5.4.a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.93-4.49 (2H, m, H-3, 5), 3.53 (2H, dd, *J* = 10.7, 9.1, H-2, 6), 2.79-2.65 (1H, m, H-4a), 1.95-1.78 (1H, m, H-4b), 1.70 (3H, s, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -191.4. Trifluoromethanesulfonic anhydride (3.7 mL, 21 mmol) was slowly added to crude product in pyridine (20 mL) at 0°C and allowed gradually to warm up to rt. After 18 h stirring at rt, the reaction mixture was quenched with a mixture of water (100 mL) and copper sulphate (2 mL) followed by extraction with DCM (100 mL x 3). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by means of column chromatography (petroleum ether/ethyl acetate 7:3) to offer **5.5.a** as a white crystalline solid (722 mg, 1.59 mmol, 30%); M.p. = 168-169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.14-4.91 (2H, m, H-3, 5), 4.74 (2H, t, *J* = 9.1 Hz, H-2, 6), 3.20-2.88 (1H, m, H-4a), 2.17-2.00 (1H, m, H-4b), 1.79 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 118.3 (q, *J* = 320.0 Hz, CF_3), 114.2 (CN), 84.9 (dd, J = 189.2, 14.7 Hz, CHF), 84.3 (d, J = 20.8 Hz, CHOTf), 41.7 (t, *J* = 6.5 Hz, C-1), 31.5 (t, *J* = 21.9 Hz, C-4), 19.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -72.7 (d, *J* = 14.2, Hz, CF_3), -189.7 (q, *J* = 12.7 Hz, CHF); IR: ν_{max}/cm^{-1} 2960 (C-H), 2873 (C-H), 2360 (C≡N), 1724, 1417 (C-C); FTMS (ESI$^+$) *m/z* calcd for ([M]+ Na$^+$) 477.9641; found 477.9638 (Δ 3.7 ppm);

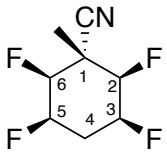
(1*R*,2*s*,3*S*,4*S*,6*R*)-2-cyano-4,6-difluoro-2-methylcyclohexane-1,3-diyl bis(trifluoromethanesulfonate) (5.5.b) and (1*R*,3*R*,4*R*,6*R*)-2-cyano-4,6-difluoro-2-methylcyclohexane-1,3-diyl bis(trifluoromethanesulfonate) (5.5.c):



Following the analogous method as described in synthesis of **5.3.a**, the mixture of the diepoxides **5.3.b** and **5.3.c** (1.5 g, 9.9 mmol) been fluorinated resulting in 1.35 g of yellow solid resulting in a mixture of **5.4.b** and **5.4.c,** which been taken for the next stage without further purification, **5.4.b** (major): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13-4.70 (2H, m, H-2, 6), 4.69-4.31 (2H, m, H-3, 5), 2.77 (1H, dd, *J* = 75.6, 4.0, H-4a), 2.54-2.17 (1H, m, H-4b); ^{19}F NMR (376 MHz, $CDCl_3$) -192.15 (s); **5.4.c** (minor): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13-4.70 (2H, m, H-2, 6), 4.69-4.31 4.34-3.90 (2H, m, H-3, 5), 2.54-2.17 (2H, m, H-4a, b); ^{19}F NMR (376 MHz, $CDCl_3$): δ -187.6 (s, br), -190.5 (s, br). Following triflation reaction, on purification using column chromatography (petrol ether/ ethyl acetate 95/5) furnishing **5.5.b** (1.82 g, 4.01 mmol, 40%)**;** M.p. = 144-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.16 (2H, dd, *J* = 9.6, 8.6 Hz, H-2, 6), 4.84 (2H, ddd, *J* = 46.6, 11.0, 8.7, Hz, H-3, 5), 2.98-2.83 (1H, m, H-4a), 2.31-2.07 (1H, m, H-4b), 1.63 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 118.9 (CN), 117.5 (q, *J* = 160.3 Hz), 83.8 (dd, *J* = 188.0, 13.7 Hz, C-3, 5), 82.4 (d, *J* = 21.3 Hz, C-2, 6), 30.7 (t, *J* = 21.8 Hz, C-4), 29.7 (C-1), 14.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -73.0 (d, *J* = 9.1 Hz, CF_3), -189.6 (s br, CHF); IR: ν_{max}/cm^{-1} 2978 (C-H), 2922 (C-H), 2360 (C≡N), 1433 (C-C), 1404 (C-C); FTMS (ESI^-) *m/z* calcd for ([M]+Cl^-) 489.9432; found 489.9429 (Δ 3.7 ppm); followed by **5.5.c** as an oily liquid (676 mg, 1.49 mmol, 15%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37-5.02 (3H, m, H-2, 3, 5), 4.87 (1H, t, *J* = 8.3 Hz, H-6), 2.93-2.76 (1H, m, H-4a), 2.30 (1H, ddtd, *J* = 38.2, 15.1, 10.6, 3.0 Hz, H-4b), 1.80 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 118.3 (q, *J* = 319.9 Hz, CF_3), 118.2 (q, *J* = 319.8 Hz, CF_3), 114.5 (CN), 85.7 (dd, *J* = 181.8, 11.6 Hz CHF), 85.1 (dd, *J* = 185.3, 2.5 Hz, CHF), 83.7 (d, *J* = 21.1 Hz, CHOTf), 81.7 (d, *J* = 28.0 Hz, CHOTf), 40.7 (d, *J* = 4.6 Hz, C-1), 31.1 (t, *J* = 21.0 Hz, C-4), 20.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -72.9 (d, *J* = 11.4 Hz, CF_3), -73.3 (d, *J* = 1.4 Hz, CF_3), -182.9 (s, CHF), -191.5 (s, CHF); IR: ν_{max}/cm^{-1} 2908 (C-H), 2341 (C≡N), 1417 (C-C); FTMS (ESI^+) *m/z* calcd for ([M]+ Na^+) 477.9641; found 477.9636 (Δ 3.7 ppm);

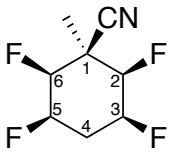


(1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexane-1-carbonitrile (5.6.a)



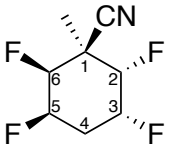
Triflate **5.5.a** (0.7 g, 1.5 mmol) and $Et_3N.3HF$ (2.68 g, 16 mmol) were placed in Teflon round bottom flask equipped with condenser and heated to 120 °C. After the full conversion of the starting material (4 days) the mixture was cooled to rt, poured into $NaHCO_3$ (150 mL) and extracted with DCM (100 mL x 3). Combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by column chromatography (Petroleum ether/ ethyl acetate 9/1) to give **5.6.a** (0.88 mg, 0.45 mmol, 30%) as a white crystalline solid, which was found to sublime under reduced pressure; M.p. = 137-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.12-4.70 (4H, m, H-2, 3, 5, 6), 2.72-2.55 (1H, m, H-4a), 2.51-2.43 (1H, m, H-4b), 1.78 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 117.0 (CN), 88.1 (d, *J* = 188.2 Hz, C-2, 6), 85.1 (d, *J* = 192.0 Hz, C-3, 5), 29.7 (C-1), 26.5 (t, *J* = 15.6 Hz, C-4), 17.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -194.5 (s br, CHF), -209.0 (s br, CHF); IR: ν_{max}/cm^{-1} 2362 (C≡N), 1244 (C-F), 1050 (C-F); FTMS (ESI$^+$) *m/z* calcd for ([M]-CH_4) 179.0358, found 179.0170 (Δ 3.7 ppm);

((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6- tetrafluoro-1-methylcyclohexane-1-carbonitrile (5.6.b)



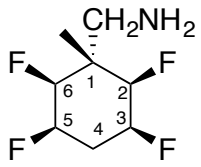
Following the analogous method as described in synthesis of **5.6.a**, triflate **5.5.b** (1.8 g, 3.96 mmol) furnished compound **5.6.b** (394 mg, 2.02 mmol, 51%) white crystalline solid; M.p. = 195 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.04 (2H, d, *J* = 50.4 Hz, H-2, 6), 4.34 (dd, *J* = 43.2, 21.5 Hz, H-3, 5), 3.01-2.72 (1H, m, H-4a), 2.12-1.85 (1H, m, H-4b), 1.77 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 116.5 (CN), 90.2 (d, *J* = 179.6 Hz, C-2, 6), 84.4 (d, *J* = 212.2 Hz, C-3, 5), 31.0 (C-1), 28.9 (C-4) , 21.3 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -198.0 (s br, CHF); IR: ν_{max}/cm^{-1} 2987 (C-H), 2358 (C≡N), 1136 (C-F), 1058 (C-F); FTMS (ESI$^+$) *m/z* calcd for ([M]+ Na^+) 218.0568; found 218.0559 (Δ 3.7 ppm);

(2*S*,3*R*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexane-1-carbonitrile (5.6.c)



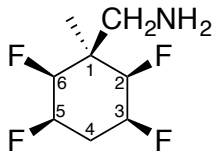
Following the analogous method as described in synthesis of **5.6.a**, triflate **5.5.c** (650 mg, 1.43 mmol) furnished compound **5.6.c** (86 mg, 0.44 mmol, 31%) white crystalline solid; M.p. = 79-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47-4.87 (3H, m, H-2, 3, 5), 4.68-4.40 (1H, m, H-6), 2.75-2.49 (1H, m, H-4a), 2.43-2.13 (1H, m, H-4b), 1.75 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 117.3 (CN), 90.5 (d, *J* = 188.9 Hz, C-2), 89.5 (dd, *J* = 180.1, 14.7 Hz, C-3), 86.4 (d, *J* = 190.8 Hz, C-5), 84.7 (d, *J* = 176.6 Hz, C-6), 29.7 (C-1), 28.8 (tt, *J* = 21.1, 5.7 Hz, C-4), 19.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ -200.2 (s br), -201.0 (s br), -206.5 (s br), -211.6 (s br); IR: ν_{max}/cm^{-1} 2991 (C-H), 2330 (C≡N), 1249 (C-F), 1074 (C-F); FTMS (ESI^+) *m/z* calcd for ([M]+ Na^+) 218.0568; found 218.0562 (Δ 3.7 ppm);

((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)methanamine (5.7.a)



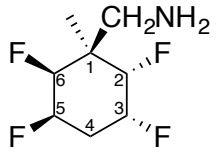
Sodium borohydride (155 mg, 4.1 mmol) was slowly added to a solution of **5.6.a** (80mg, 0.41 mmol) and nickel-(II) chloride hexahydrate (264 mg, 2.05 mmol) in methanol (5 mL) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and was stirred until disappearance of starting material (TLC). Methanol was evaporated under vacuum, and the resulting crude was diluted with ethyl acetate (100 mL). Then, an aqueous saturated solution of $NaHCO_3$ was added (50 mL). The resulting mixture was filtered through a pad of Celite, and the solution was extracted with ethyl acetate (4 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was purified using column chromatography to furnish **5.7.a** as a white solid (41 mg, 2.05 mmol, 50%); M.p. = 99-100 °C; ^{1}H NMR (400 MHz, MeOD): δ 5.09-4.98 (2H, m, H-2, 6), 4.58 (2H, dd, *J* = 45.0, 20.5, Hz, H-3, 5), 2.78 (2H, s, CH_2), 2.63-2.43 (1H, m, H-4a), 2.23-2.01 (1H, m, H-4b), 1.31 (3H, t, *J* = 1.6 Hz, CH_3); ^{13}C NMR (101 MHz, MeOD): δ 94.2 (dd, *J* = 185.7, 16.4 Hz), 90.1 (dd, *J* = 183.3, 15.0 Hz). 49.3 (CH_2), 32.1 (C-4), 27.5 (C-1), 16.6 (CH_3); ^{19}F NMR (376 MHz, MeOD): δ -196.6 (s br) , -209.5 (s br); IR: ν_{max}/cm^{-1} 3520 (N-H), 2972(C-H), 2901 (C-H), 2358, 1734 (N-H), 1417 (C-H); 1215 (C-F); FTMS (ESI^+) *m/z* calcd for ([M]+H) 200.1062; found 200.1051 (Δ 3.7 ppm);

((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)methanamine (5.7.b)



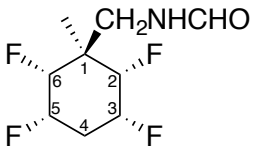
Following the analogous method as described in synthesis of **5.7.a**, tetrafluoro nitrile **5.6.b** (350 mg, 1.79 mmol) provided a tetrafluoro amine **5.7.b** (225 mg, 1.13 mmol, 65%) white crystalline solid; M.p. = 106-107 °C; ^{1}H NMR (500 MHz, MeOD): δ 5.00-4.71 (2H, m, H-2, 6), 4.67 (4H, dm, *J* = 49.8, H-3, 5), 3.09 (2H, s, CH_2-N), 2.61-2.39 (2H, m, H-4), 0.99 (3H, s, CH_3); ^{13}C NMR (126 MHz, MeOD): δ 90.6 (dd, *J* = 193.2, 12.9 Hz, C-2, 6), 85.8 (dd, *J* = 181.4, 14.7 Hz, C-3, 5), 43.4 (CH_2NH_2), 27.5 (t, *J* = 21.8 Hz, C-4), 22.7 (C-1), 14.9 (CH_3); ^{19}F NMR (377 MHz, MeOD): δ -196.5 (m, AA'XX'), -209.3 (s br); IR: ν_{max}/cm^{-1} 3510 (N-H), 2972 (C-H), 2900 (C-H), 2357, 1595 (N-H), 1222 (C-F); FTMS (ESI^{+}) *m/z* calcd for ([M]+H) 200.1062; found 200.1051 (Δ 3.7 ppm);

((2*S*,3*R*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)methanamine (5.7.c)



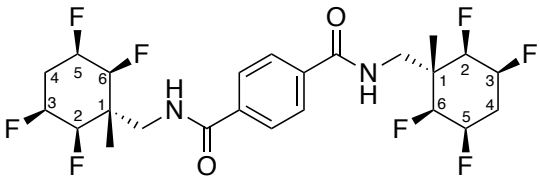
Following the analogous method as described in synthesis of **5.7.a**, tetrafluoro nitrile **5.6.c** (80 mg, 0.41 mmol) provided a tetrafluoro amine **5.7.c** as colourless oil (19 mg, 0.094 mmol, 23%); ^{1}H NMR (400 MHz, MeOD): δ 5.25-4.79 (3H, m, H-2, 3, 5), 4.65 (1H, dd, *J* = 45.1, 26.4, H-6), 2.93 (1H, d, *J* =13.5, CH_{2a}), 2.82 (1H, dt, *J* =13.5, 2.3, CH_{2b}), 2.53-2.11 (2H, m, H-4), 1.17 (3H, s, CH_3); ^{13}C NMR (126 MHz, MeOD): δ 93.1 (dd, *J* = 180.5, 5.8 Hz, C-3, 5), 92.4 (dd, *J* = 180.6, 5.8 Hz, C-2, 6), 46.0 (CH_2), 28.7 (t, *J* = 21.2, 6.5 Hz, C-4), 22.8 (C-1), 13.7 (CH_3); ^{19}F NMR (377 MHz, MeOD): δ -197.9 (s br), -201.8 (s br), -213.4 (s br), -215.4 (s br); IR: ν_{max}/cm^{-1} 3525 (N-H), 2972 (C-H), 2893 (C-H), 2358, 2343, 1558 (N-H), 1069 (C-F); FTMS (ESI^{+}) *m/z* calcd. for ([M]+H) 200.1062; found 200.1052 (Δ 3.7 ppm);

***N*-(((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)methyl)formamide (5.8)**



`Following literature described method, to a solution of tetrafluoro nitrile **5.6.a** (110 mg, 0.56 mmol) in THF (5 mL) a mixture of formic acid and triethalamine with molar ratio of 37: 1 (1 mL) was added under argon atmosphere. After the addition of Pd/C (10 mol%), the mixture was degased, flushed three times with H_2, and left stirring under H_2 atmosphere at room temperature until completion (TLC monitoring). The reaction mixture was passed through a pad of celite. The filtrate was concentrated and purified using column chromatography (petrol ether/ diethyl ether 75/ 25) resulting in **5.8** (99 mg, 0.43 mmol, 78% yield) as a white crystalline solid; M.p.= 146-147 °C; ^{1}H NMR (400 MHz, MeOD): δ 8.16 (1H, s, CHO), 5.05 (d, *J* = 45.3 Hz, H-3, 5), 4.43 (2H, dd, *J* = 43.6, 15.6 Hz, H-2, 6), 3.23 (2H, s br, CH_2-N), 2.55-2.38 (1H, m, H-4a), 2.29-2.08 (1H, m, H-4b), 1.28 (3H, s, CH_3); ^{13}C NMR (101 MHz, MeOD): δ 163.1 (CHO), 89.2 (dd, *J* = 188.4, 12.9 Hz, C-3, 5), 85.9 (dd, *J* = 177.1, 13.4 Hz, C-2,6), 43.6 (C-1), 40.6 (CH_2-NH_2), 27.5 (C-4), 13.9 (CH_3); ^{19}F NMR (376 MHz, MeOD): δ -196.5 (s br), -210.7 (s br); IR: ν_{max}/cm^{-1} 3246 (N-H), 3064 (OC-H), 1653 (C=O); FTMS (ESI^{+}) *m/z* calcd for ([M]+Na^{+}) 250.0831; found 250.0825 (Δ 3.7 ppm);

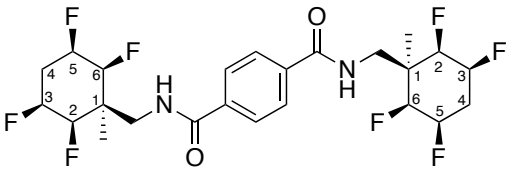
bis(((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)methyl)terephthalamide (5.9)



Tetrafluorocyclohexane amine **5.7.a** (30 mg, 0.15 mmol) and DMAP (2 mg, 0.016 mmol) were dissolved in DCM under argon atmosphere followed by addition of Et_3N (30 mg, 0.3 mmol). After cooling to 0 °C, tetephnaloyol chloride (16 mg, 0.075 mmol) was added and the mixture was stirred for 15 min at 0 °C and for further 18 h at room temperature. After the reaction was complete, water was added and the solution was extracted three times with DCM. The combined organic phases were dried over $MgSO_4$ filtered and the solvent was removed under reduced pressure. The product was purified by column chromatography (petroleum ether/ diethyl ether, 9/1) furnishing **5.9** (31 mg, 0.59 mmol, 79%); M.p. = 292-293°C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.02 (4H, s, Ar), 5.46-5.12 (4H, m, H-2, 6), 4.67 (4H, dd, *J* = 46.8, 11.7, H-3, 5), 3.46 (4H, s, CH_2), 2.54-2.27 (4H, m, H-4), 1.47 (6H, m, CH_3); ^{13}C (126 MHz, $(CD_3)_2CO$): δ 166.9 (COAr), 136.8 (C(Ar)), 127.4 (CH(Ar)), 90.6 (dd, *J*=186.9, 12.8, C-2,6), 86.4 (dd, *J* = 194.6, 12.3, C-3, 5), 44.5 (C-1), 42.3 (CH_2) , 27.4 (C-4), 15.5 (CH_3); ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ -195.4 (s br), -210.1 (s br); IR: ν_{max}/cm^{-1} 3329 (N-H),

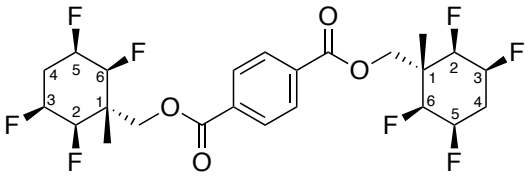
2953 (C-H), 1639 (C=O); FTMS (ESI^-) *m/z* calcd for ([M]- H^+) 527.1944; found 527.1946 (Δ 3.7 ppm);

bis(((1*r*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)methyl)terephthalamide (5.10)



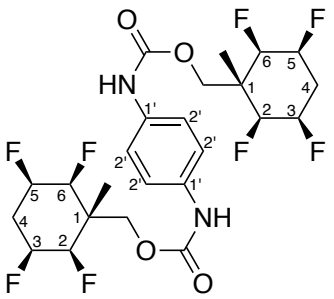
Following analogous proceedure as in synthesis of **5.9**, tetrafluoro amine (**5.7.b**) was used to furnish **5.10** (19 mg, 0.036 mmol, 48%) as a white crystalline solid; M.p. = 167 °C; ^1H NMR (400 MHz, CD_3CN): δ 7.92 (4H, s, H (Ar)), 7.13 (2H, t, *J* = 6.8, NH), 5.14-4.64 (4H, m, H- 2, 3, 5, 6), 3.81 (4H, d, *J* = 6.7, CH_2-NH), 2.54-2.35 (4H, m, H-4), 0.93 (3H, t, *J* = 1.4, CH_3); ^{13}C NMR (101 MHz, CD_3CN): δ 167.0 (COAr), 137.2 (C- (Ar)), 127.4 (CH (Ar)) , 90.4 (d, *J* = 89.2, C- 2, 6), 85.9 (d, *J* = 196.2, C-3, 5), 42.4 (C-1), 41.2 (CH_2-NH), 27.5 (C-4), 15.6 (CH_3); ^{19}F NMR (376 MHz, CD_3CN): δ -195.5 (AA'XX'), -207.8 (s br); IR: ν_{max}/cm^{-1} 3320 (N-H), 2924 (C-H), 1730 (C=O); FTMS (ESI^+) *m/z* calcd for ([M] + Na^+) 551.1920; found 551.1915 (Δ 3.7 ppm);

bis(((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)methyl) terephthalate (5.11)



Analogous esterification reaction has been done with tetephnaloyol chloride and 2,3,4,5-tetrafluoro alcohol **3.9.a**, which has been previously reported in Chapter 3, resulting in compound **5.11** (0.032 g, 0.06 mmol, 88%) as white solid; M.p. = 257 °C; ^1H NMR (500 MHz, $(CD_3)_2CO$): δ 8.20 (4H, s, Ar), 5.19 (4H, ddt, *J* = 47.6, 10.6, 3.1 Hz, H- 3, 5), 4.93 (4H, ddd, *J* = 44.3, 22.2, 3.2 Hz, H- 2, 6), 4.35 (4H, s, CH_2), 1.41 (6H, s, CH_3); ^{13}C NMR (126 MHz, $(CD_3)_2CO$): δ 164.7 (s, C(O)O), 133.9 (C-1'), 129.7 (C-2'), 88.8 (d, *J* = 183.9 Hz, C-3), 86.9 (d, *J* = 183.8 Hz, C-2), 65.0 (CH_2), 43.2 (s, C-4), 39.3 (s, C-1) 29.4 (s, CH_3); ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ -195.7 (s br, F-3), -209.4 (s br, F-2); IR: ν_{max}/cm^{-1} 1728 (C=O), 1267, 1244 (C-O); FTMS (ESI^-) *m/z* calcd for ([M]+Cl^-) 565.1392; found 565.1396 (Δ 3.7 ppm);

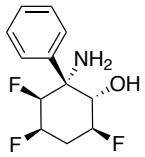
bis(((1*s*,2*R*,3*S*,5*R*,6*S*)-2,3,5,6-tetrafluoro-1-methylcyclohexyl)methyl) 1,4-phenylenedicarbamate (5.12)



1,4-Phenylene diisocyanate (12 mg, 0.075 mmol) has been combined with previously prepared tetrafluor alcohol derivative **3.9.a** (30 mg, 0.15 mmol), followed by addition of toluene (2 mL) and triethalamine (0.005 g, 0.05 mmol). The reaction has been left stirring over night, followed by heating the reaction at 60 °C for 4 hours. On the completion, the solvent has been evaporated, resulting in yellow powder **5.12** (62 mg, 0.011 mmol, 91%); M.p.= 273 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.45 (4H, s, H-2'), 5.14 (4H, dd, *J* = 47.3, 15.1 Hz, H-3), 4.78 (dd, *J* = 47.3, 15.5 Hz, H-2), 4.12 (2H, s, CH_2), 2.51(2H, m, H-4a), 2.25 (2H,m, H-4b), 1.33 (3H, s, CH_3); ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 152.8 (s, C(O)O) , 134.1 (s, C-1') , 119.0 (C-2'), 89.4 (d, *J* = 170.8 Hz, C-3), 86.8 (d, *J* = 182.3 Hz, C-2), 43.3 (t, *J* = 18.6 Hz, C-4), 27.7 (s, C-1), 13.2 (CH_3); ^{19}F NMR (376 MHz, $(CD_3)_2CO$): δ -194.9 (s (br), F-3), -209.0 (s, F-2); FTMS (ESI^-) *m/z* calcd for ([M]-H) 559.184; found 559.184 (Δ 3.7 ppm);

7.3. Additional experimental for Chapter 2.

7.3.1. 1D selective ^{1}H, ^{19}F HOESY (C, D, E, F): amino alcohol 2.14.a.



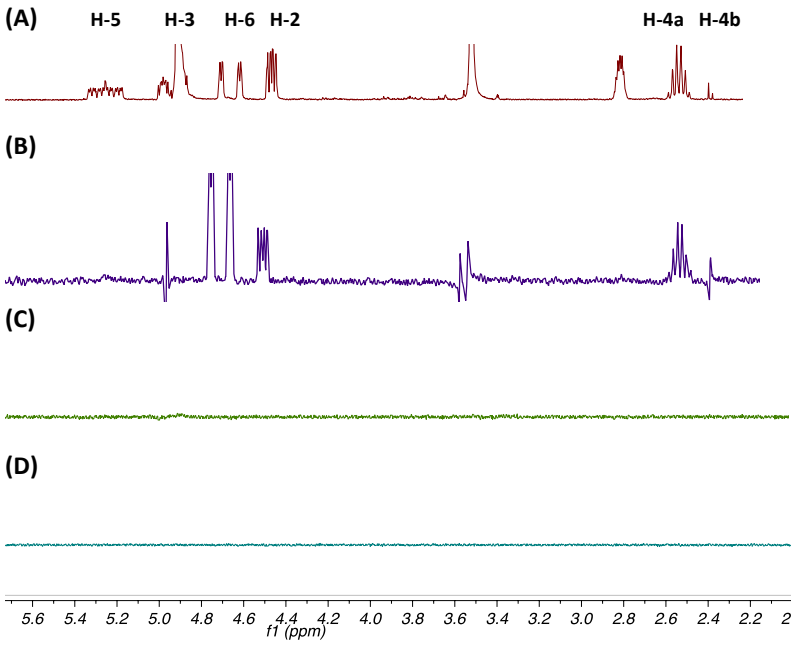


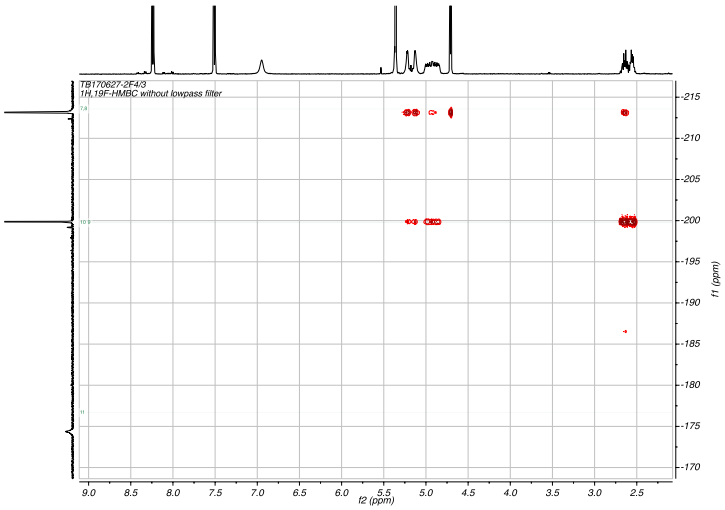
Figure 1: A) ^{1}H NMR Spectrum of 2.14.a in MeOD; B) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-6 at rt. C) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-5. F) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-3.

7.3.2. (A) ^{1}H, ^{19}F NMR HMBC; (B) ^{19}F observe with ^{1}H decoupling; (C) 1D selective ^{1}H, ^{19}F HOESY (C, D, E, F): carboxamide 2.34.

2D ^{19}F HMBC and 1D ^{19}F with ^{1}H decoupling and 1D selective ^{1}H, ^{19}F-HOESY spectra were recorded using Bruker AVANCE 500 MHz spectrometer equipped with 5 mm QNP-probe at RT.

4-bromobenzyl-1,2,3,5,6-pentafluorocyclohexane-1-carboxamide (2.34)

1. A) ^{1}H, ^{19}F (500 MHz, CD_2Cl_2) HMBC NMR



1. B) ^{19}F (500 MHz, CD_2Cl_2) with ^{1}H decoupling NMR, SW 80 ppm

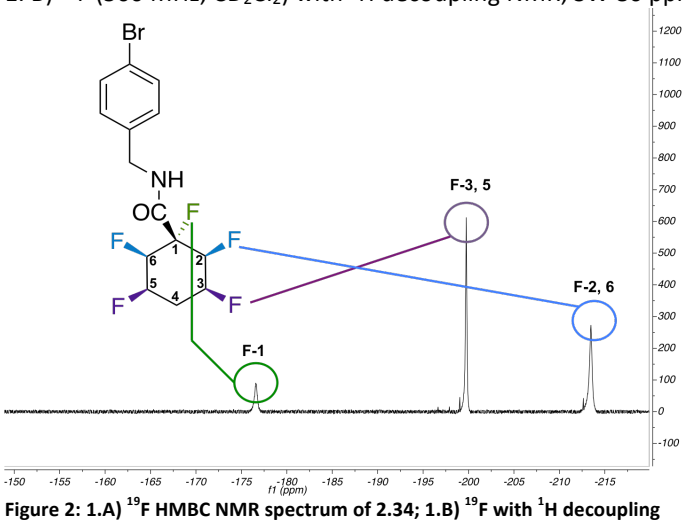


Figure 2: 1.A) ^{19}F HMBC NMR spectrum of 2.34; 1.B) ^{19}F with ^{1}H decoupling NMR spectrum of 2.34 along with the structure of 2.34, identifying the 3 fluorine peaks that relate to F-1, 2, 3, 5, 6 fluorine atoms.

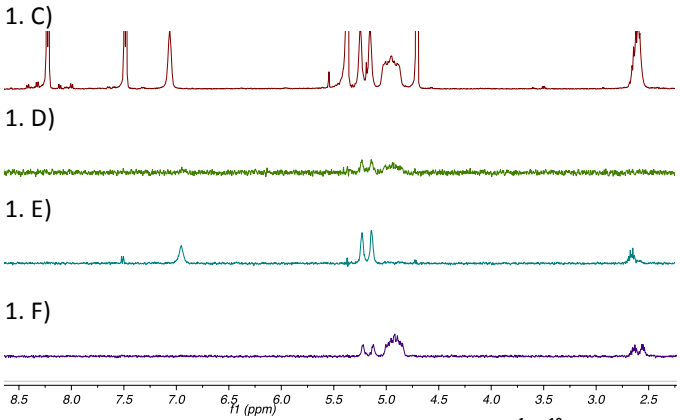
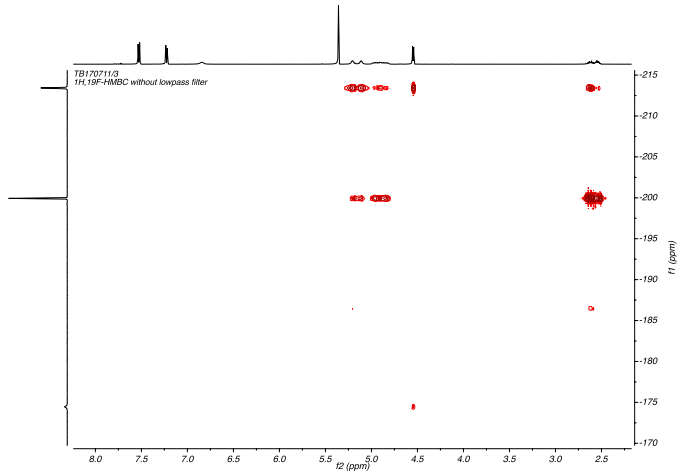


Figure 3: 1.C) 1H NMR Spectrum of 2.34. 1.D) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-1; 1.E) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-2 and F-6; 1.F) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-3 and F-5.

7.3.3. (A) ^{1}H, ^{19}F NMR HMBC; (B) ^{19}F observe with ^{1}H decoupling; (C) 1D selective ^{1}H, ^{19}F HOESY (C, D, E, F): carboxamide 2.37.

1,2,3,5,6-pentafluoro- 4-nitrobenzyl cyclohexane-1-carboxamide (2.37)

2. A) ^{1}H, ^{19}F (500 MHz, CD_2Cl_2) HMBC NMR



2. B)

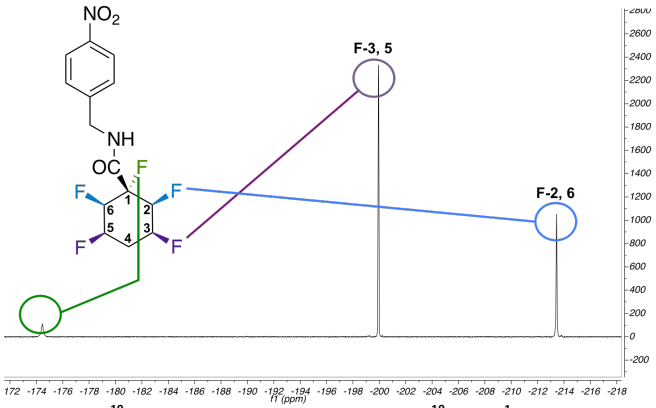


Figure 4: A) ^{19}F HMBC NMR spectrum of 2.37. B) ^{19}F with ^{1}H decoupling NMR spectrum of 2.37 along with the structure of 2.37, identifying the 3 fluorine peaks that relate to F-1, 2, 3, 5, 6 fluorine atoms.

2. C)

2. D)

2. E)

2. F)

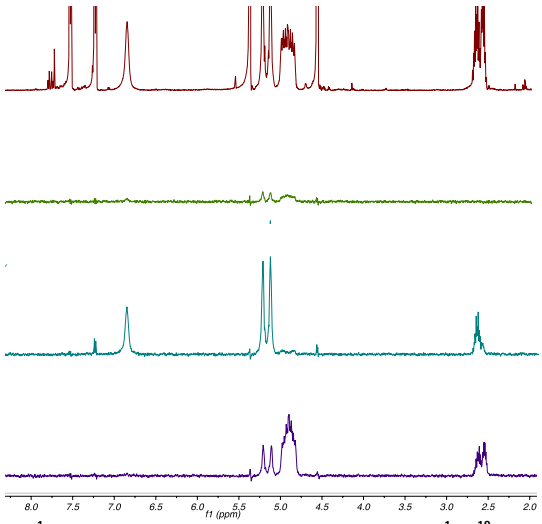
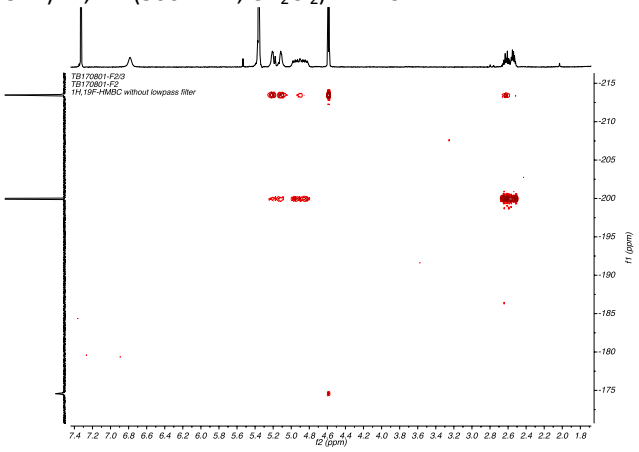


Figure 5: 2.C) ^{1}H NMR Spectrum of 2.37; 2.D) 1D selective ^{1}H, ^{19}F-HOESY with increased number of scans up to 800, irradiation of F-1; 2.E) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-2 and F-6. 2.F) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-3 and F-5

7.3.4. (A) ^{1}H, ^{19}F NMR HMBC; (B) ^{19}F observe with ^{1}H decoupling; (C) 1D selective ^{1}H, ^{19}F HOESY (C, D, E, F): carboxamide 2.35.

1,4-phenylenebis(methylene)bis-1,2,3,5,6-pentafluorocyclohexane-1-carboxamide (2.35)

3. A) ^{1}H, ^{19}F (500 MHz, CD_2Cl_2) HMBC NMR



3. B)

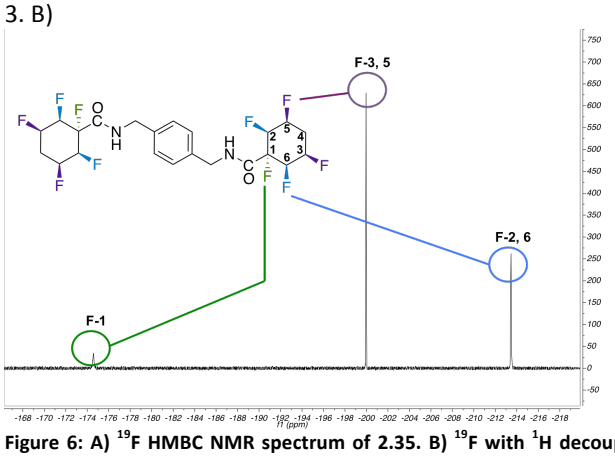
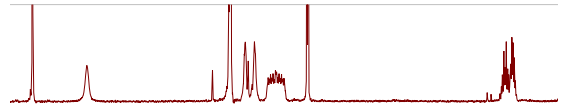


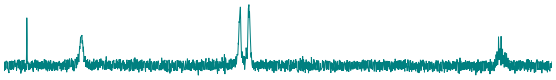
Figure 6: A) ^{19}F HMBC NMR spectrum of 2.35. B) ^{19}F with ^{1}H decoupling NMR spectrum of 2.35 along with the structure of 16, identifying the 3 fluorine peaks that relate to F-1, 2, 3, 5, 6 fluorine atoms.

3. C)



3. D)

3. E)



3. F)

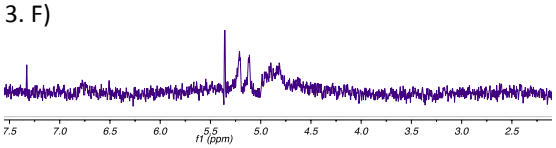


Figure 7: 3.C) 1H NMR Spectrum of 2.35. 3.D) 1D selective ^{1}H, ^{19}F-HOESY with increased number of scans up to 800: Irradiation of F-1; 3.E) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-2 and F-6; 3.F) 1D selective ^{1}H, ^{19}F-HOESY: Irradiation of F-3 and F-5.

7.3.5: Density Functional Theory Computations

A conformational analysis was performed for a model amide at the B3LYP[vii]/6-311+G** level of density functional theory.[13–16] Starting from the X-ray derived coordinates for the N-(p-Br)-benzyl and N-benzyl derivatives, which have the amide in equatorial and axial positions, respectively, truncated models were built by replacing the benzyl substituent with a methyl group. After initial optimisation to the minima **eq1** and **ax1**, full rotational profiles were constructed through relaxed scans of the F-C-C=O dihedral angles (θ). The resulting profiles are displayed in Figure 8.

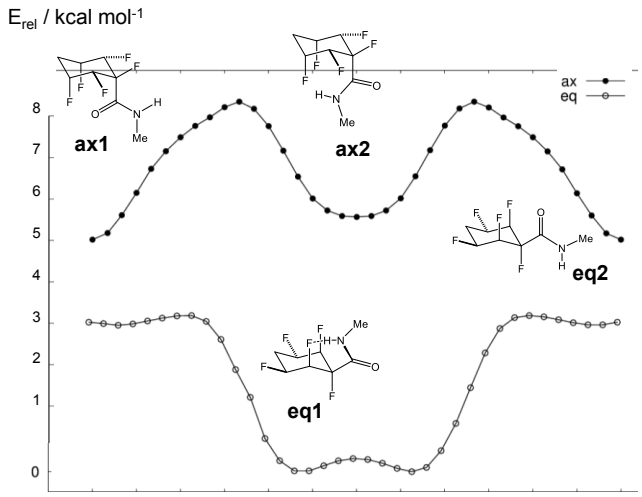
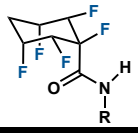
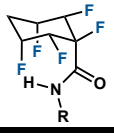
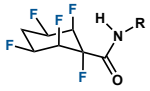
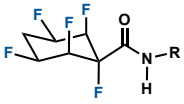


Figure 8: Rotational profiles about the C(F)-C(=O) bond in a simpler model for the target compounds (R = Me, B3LYP/6-311+G level), energies given in kcal mol-1 relative to the most stable conformer (eq1).**

On these profiles, higher-lying minima were apparent, which were subjected to full geometry optimisations, affording rotamers **ax2** and **eq2**. Relative energies and salient geometrical parameters of all minima are collected in Table 1. Conformations **ax1** and **ax2** are essentially C_s-symmetric with dihedral angles θ of 180° and 0°, respectively, **eq1** and **eq2** are lacking such planes of symmetry and come in enantiomeric pairs (though separated by very low barriers, cf. lower profile in Figure 8).

Table 1: Computed properties (energies ΔErel relative to eq1, dipole moments m, selected angles and distances) of model amide compounds at the B3LYP/6-311+G level (gas phase values, unless otherwise noted).**

Property	Conformer of α-fluoroamide **2.33**			
	ax1	**ax2**	**eq1**	**eq2**
				
ΔE_{rel} [kcal mol^{-1}] gas phase (ΔE_{rel} [kcal mol^{-1}] in water) [a]	5.6 (0.3)	6.1 (0.9)	0.0 (0.0)	3.5 (0.6)
$\theta_{F\text{-}C\text{-}C=O}$ calc [°]	179.9	-1.7	37.6	163.7
X-ray	*161.1* [b]	*n.a.*	*5.8* [c]	*n.a.*
nearest $d_{F\cdots H(N)}$ [Å] [d]	2.084	2.141	1.991	2.112
μ [D]	4.9	7.2	2.1	6.4

[a]CPCM method. [b]N-(p-Br-benzyl), this work. [c]N-Benzyl derivative derivative, this work. [d]Distance between NH proton and nearest F atom.

The relaxed scan and subsequent optimisations were repeated using a simple solvent model, namely the polarizable conductor variant of the polarizable continuum model (CPCM), employing the parameters of water and the default options in Gaussian 09. [17,18]

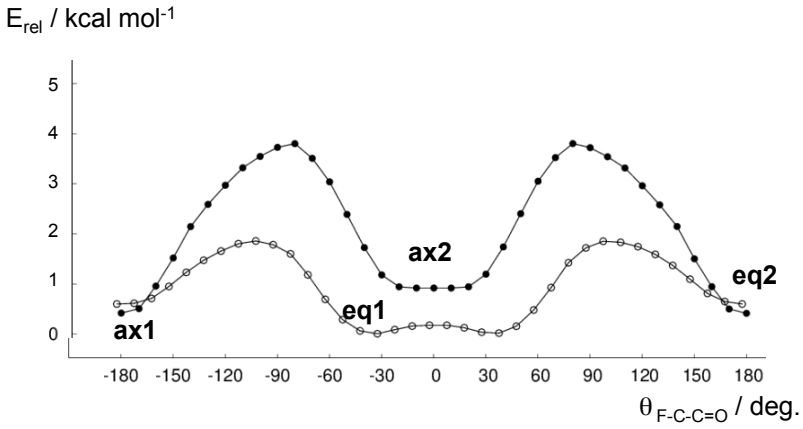


Figure 9: Rotational profiles about the C(F)-C(=O) bond in a simpler model for the target compounds in a continuum modeling water(R = Me, CPCM/B3LYP/6-311+G level), energies given in kcal mol-1 relative to the most stable conformer (eq1).**

Coordinates of the DFT-optimised structures

Cartesian coordinates in Å, B3LYP/6-311+G** optimised (xyz format)

ax1

F,0,0.9687001115,7.436209174,3.9340216595
F,0,2.664408351,6.8014625287,6.177233602
F,0,1.6219930437,4.4706040042,7.2197199292
F,0,-0.90835014,3.7992726836,5.74120872
F,0,-1.3568685499,5.7330169911,3.8274539268
O,0,-0.5150795221,6.3522242234,6.9684756659
N,0,-0.4224530984,8.3491946315,5.8888072802
C,0,0.6855581596,6.4112198459,4.8827848051
C,0,2.0630552146,5.8873895557,5.3223816603
H,0,2.6730660482,5.8616260576,4.4115871679
C,0,2.1159707985,4.4834923049,5.9267438207
H,0,3.171156527,4.2002903101,5.9983717421
C,0,1.3645643871,3.4771269083,5.0543218768
H,0,1.9448831401,3.3019547365,4.140983936
H,0,1.3081420183,2.5241191351,5.583756497
C,0,-0.0488751048,3.9088415126,4.6615875504
H,0,-0.441386764,3.2411635999,3.8877370028
C,0,-0.0549769937,5.325166946,4.0845758149
H,0,0.4546438599,5.2728743205,3.1150817183
C,0,-0.1518682918,7.0342877689,6.0342007836
C,0,-1.188890387,9.0669434972,6.8974679838
H,0,-2.1223512113,8.5415629492,7.1065195707
H,0,-1.4130519204,10.0645901549,6.5210290255
H,0,-0.0594287869,8.8356599648,5.0857497228
H,0,-0.6284100192,9.1518113955,7.8322360279

ax2

F,0,0.6063631172,1.037763822,2.1005786926
F,0,0.273277177,2.4196218923,-0.4579074744
F,0,-1.0081311473,0.5515410109,-2.0079589305
F,0,-1.1490351734,-1.9217274347,-0.717831749
F,0,0.053391708,-1.8145591667,1.7440258838
O,0,2.6245344837,0.2781450021,0.757224913
N,0,1.4804928735,-0.6304713407,-0.9700758452
C,0,0.2228887813,0.4337527156,0.9009069394
C,0,-0.5862117704,1.5192451156,0.1540788209
H,0,-1.1245196191,2.073845928,0.9315211245
C,0,-1.6307411742,1.0483283277,-0.8542324405
H,0,-2.2113700097,1.9157029407,-1.1770399668
C,0,-2.5357368126,-0.0294185207,-0.2661636853
H,0,-3.157335237,0.4150666379,0.5189466324
H,0,-3.2114505201,-0.3978916504,-1.0404498936
C,0,-1.7535548343,-1.1990044989,0.321954691
H,0,-2.4185750502,-1.9037425742,0.8263350388
C,0,-0.7028038502,-0.7292511649,1.3256241225
H,0,-1.2480815798,-0.365804607,2.2044271715
C,0,1.576170082,0.0100015669,0.2101339678
C,0,2.6790631555,-1.051933763,-1.6831206036
H,0,3.3321856856,-0.1979840272,-1.8740124429

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H,0,3.2403347082,-1.7887248116,-1.1033478063

eq1

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F,0,3.0792548989,5.4476255642,9.137557586
F,0,2.4078736025,4.0575457119,6.8630105668
O,0,0.1551481443,5.8223032644,4.6568484188
N,0,-0.0090953905,3.5569847275,4.7445319578
C,0,0.170767335,4.8724213854,6.8469830284
C,0,-0.5013868216,3.7384479763,7.6548695512
H,0,-1.5603586262,3.6764621142,7.3961642108
C,0,-0.3238083402,3.9591473592,9.154739927
H,0,-0.8964812632,4.8469762622,9.4366879916
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H,0,1.993077437,6.0295578723,6.7671534642
C,0,0.0999473254,4.7862544225,5.2923389187
C,0,0.026122627,3.3797808187,3.2971054988
H,0,-0.6575192963,4.0839434792,2.8234265463
H,0,-0.2838185462,2.3618159747,3.0628948845
H,0,0.0920001249,2.7485138004,5.339756838
H,0,1.0296603239,3.5532601225,2.8979114794

eq2

F,0,-0.5115157648,-0.0616232962,1.7202083571
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F,0,2.198955942,-2.5413937879,-0.1121860611
F,0,2.5971410692,2.2008943403,0.3613981013
F,0,0.5573365278,1.5140415939,-1.3182873908
O,0,-2.1335604152,0.6166092962,-1.3466300727
N,0,-2.8663306791,-0.1880920589,0.6540616046
C,0,-0.463553548,0.0569048505,0.3002477316
C,0,0.1976974837,-1.2637926782,-0.1705028842
H,0,-0.4132749572,-2.1094635503,0.1573042887
C,0,1.6138071464,-1.3823664906,0.3992564504
H,0,1.5360662415,-1.5222926765,1.4812822959
C,0,2.4772630857,-0.1705112391,0.0689861298
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H,0,-0.0493015617,2.1849025645,0.4749219635
C,0,-1.9108791699,0.2101629145,-0.2248252498
C,0,-4.2825982798,-0.1015869442,0.3209081494
H,0,-4.6729850585,0.9095328367,0.4714513005
H,0,-4.8380708728,-0.797846267,0.9495349709

H,0,-2.5940557341,-0.3943773858,1.6021028382
H,0,-4.4211102594,-0.3693655293,-0.725875252

ax1 (in water)
F,0,1.0128642494,0.029359834,2.003224109
F,0,0.175880595,2.4032669388,0.547913929
F,0,-1.5366920137,1.4976302468,-1.3853889707
F,0,-1.488833498,-1.4922632027,-1.3833734835
F,0,0.2262655666,-2.3658645543,0.55732803
O,0,0.9671120318,0.0610038708,-1.5426158307
N,0,2.614799167,-0.0131621994,0.0159205236
C,0,0.2905509124,0.0200553237,0.7766543251
C,0,-0.6003398752,1.2744234537,0.8258713964
H,0,-0.9327236447,1.3685527486,1.8637492215
C,0,-1.8589074287,1.2794253487,-0.0389855959
H,0,-2.4680471077,2.1332680363,0.2637335688
C,0,-2.6519731498,-0.0130419099,0.117107351
H,0,-3.111063551,-0.0190003758,1.1104170707
H,0,-3.4703559384,-0.0227542527,-0.6046160534
C,0,-1.8277238131,-1.2858528929,-0.0387656991
H,0,-2.4181534641,-2.1551482864,0.2573469278
C,0,-0.5743343784,-1.2527571528,0.8309061569
H,0,-0.9063105406,-1.3510704543,1.8681652931
C,0,1.3328313846,0.0264329318,-0.3767237932
C,0,3.708989568,-0.0222460384,-0.9479323478
H,0,3.627249269,-0.8817359571,-1.6164561423
H,0,4.6473151428,-0.0831070199,-0.4003916443
H,0,2.823366429,-0.035193038,1.0018119485
H,0,3.7039000876,0.8887836014,-1.5502762906

ax2 (in water)
F,0,0.6433059045,0.8491787873,2.1783674686
F,0,0.2243126736,2.480807881,-0.2088935564
F,0,-1.0210263812,0.7597245116,-1.92345668
F,0,-1.1054489609,-1.8620001155,-0.8851706582
F,0,0.1361242458,-1.9497460048,1.5526855646
O,0,2.6152940648,0.4324363196,0.6411573885
N,0,1.4547652406,-0.5719489476,-1.0181291508
C,0,0.2189184228,0.3668895287,0.9286419955
C,0,-0.6273451033,1.5070783013,0.3214148022
H,0,-1.1609754132,1.9742145558,1.1534937781
C,0,-1.6682658725,1.114331092,-0.7208210634
H,0,-2.2772358259,1.9889216207,-0.9517300017
C,0,-2.5351540189,-0.0438902732,-0.2466361459
H,0,-3.1698761192,0.3012633398,0.5749467123
H,0,-3.2033370758,-0.3518882168,-1.0522268681
C,0,-1.728347028,-1.243995589,0.22702511
H,0,-2.3740736843,-2.0064942389,0.6622649653
C,0,-0.6736882728,-0.8497545256,1.2556781263
H,0,-1.210898735,-0.5958086699,2.1734714122
C,0,1.5545880042,0.0648101134,0.1532463716
C,0,2.6339148646,-0.8729297284,-1.8236394329
H,0,3.1689768252,0.0429938891,-2.0819265093
H,0,2.3064196552,-1.3654659019,-2.7371184044
H,0,0.5539689902,-0.8786265974,-1.3542849258
H,0,3.3157125995,-1.5343721313,-1.2845922982

eq1 (in water)

F,0,-0.1318400542,0.307937789,1.991198065
F,0,-0.011610757,-1.5846070581,-1.0396031143
F,0,2.2736461447,-2.4700040595,0.1246407875
F,0,2.4200433903,2.2461498108,-0.6516457159
F,0,0.027415428,1.2096685911,-1.4578901804
O,0,-2.5271674933,1.0385011323,1.1744133695
N,0,-2.5165871314,-0.4975666088,-0.4956196696
C,0,-0.389355205,0.1166215195,0.625088266
C,0,0.2436490716,-1.2580890409,0.3058042275
H,0,-0.2163883116,-2.03419464,0.9184412263
C,0,1.7551957713,-1.2234794252,0.5096228375
H,0,1.959991826,-1.1153763277,1.5764334538
C,0,2.4258944889,-0.1203729999,-0.3001417778
H,0,3.4986405481,-0.1225658357,-0.1034181915
H,0,2.264944742,-0.2912208289,-1.3666933101
C,0,1.8326879933,1.2222113174,0.1087554812
H,0,2.0488933736,1.4458957868,1.1557130718
C,0,0.3221455992,1.2879081813,-0.0914884088
H,0,-0.0806491566,2.2319748061,0.2780636142
C,0,-1.932755237,0.2456845555,0.4526492727
C,0,-3.9471927396,-0.3997721491,-0.7715015715
H,0,-4.528921794,-0.6779996059,0.1091256938
H,0,-4.1848134358,-1.0798176609,-1.5867926543
H,0,-1.9496678619,-1.1012444136,-1.0723727497
H,0,-4.2159471996,0.6182061641,-1.0611140227

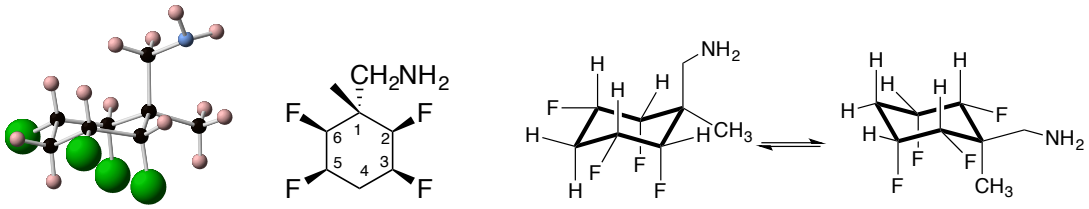
25

eq2 (in water)

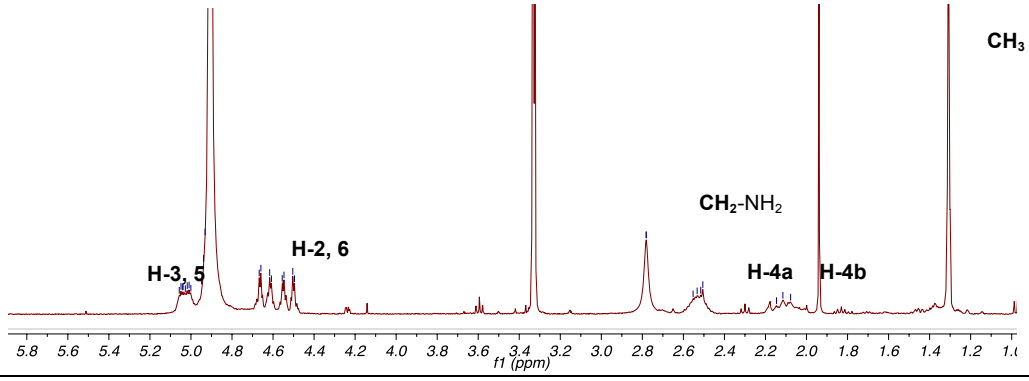
F,0,-0.5176987715,0.0070149109,1.7164229509
F,0,0.3868302015,-1.3969797578,-1.4503755882
F,0,2.3645399466,-2.4155339174,0.097053703
F,0,2.4375616356,2.3629486638,0.1497673205
F,0,0.4454177017,1.4238285161,-1.4292222319
O,0,-2.1329273978,0.1043457083,-1.4475002986
N,0,-2.8819789716,-0.0258669238,0.6929584393
C,0,-0.474099677,0.0168585745,0.301687875
C,0,0.2843822196,-1.2844382204,-0.0651707017
H,0,-0.2761337524,-2.1488831762,0.2950745614
C,0,1.690952873,-1.2633638887,0.5349346518
H,0,1.6100047052,-1.3438897824,1.6202740957
C,0,2.4838259608,-0.0275261802,0.126401411
H,0,3.4640032695,-0.0468676527,0.6046095155
H,0,2.6228307082,-0.0181356867,-0.9568901436
C,0,1.7275146795,1.2226623067,0.5605265623
H,0,1.6446515689,1.282062622,1.6469948569
C,0,0.3262603905,1.2978629247,-0.0466784957
H,0,-0.2085087336,2.1757716854,0.3198714074
C,0,-1.9216875648,0.0391510543,-0.2418340062
C,0,-4.2968560732,-0.0226850727,0.3361370923
H,0,-4.57091494,0.9126332831,-0.1566197405
H,0,-4.8805246925,-0.1311158184,1.2478237326
H,0,-2.6203123875,-0.0656081098,1.6662482153
H,0,-4.524021899,-0.8513980626,-0.3369861845

7.4: Additional NMR experimental data Chapter 5.

7.4.1. (A) ^{1}H NMR; (B) 2D ^{1}H-DQF-COSY; (C) 1D selective ^{1}H, NOESY for methanamine (5.7.a)



(A) *^{1}H (500 MHz, MeOD)*



(B) *2D ^{1}H-DQF-COSY (500 MHz, MeOD)*

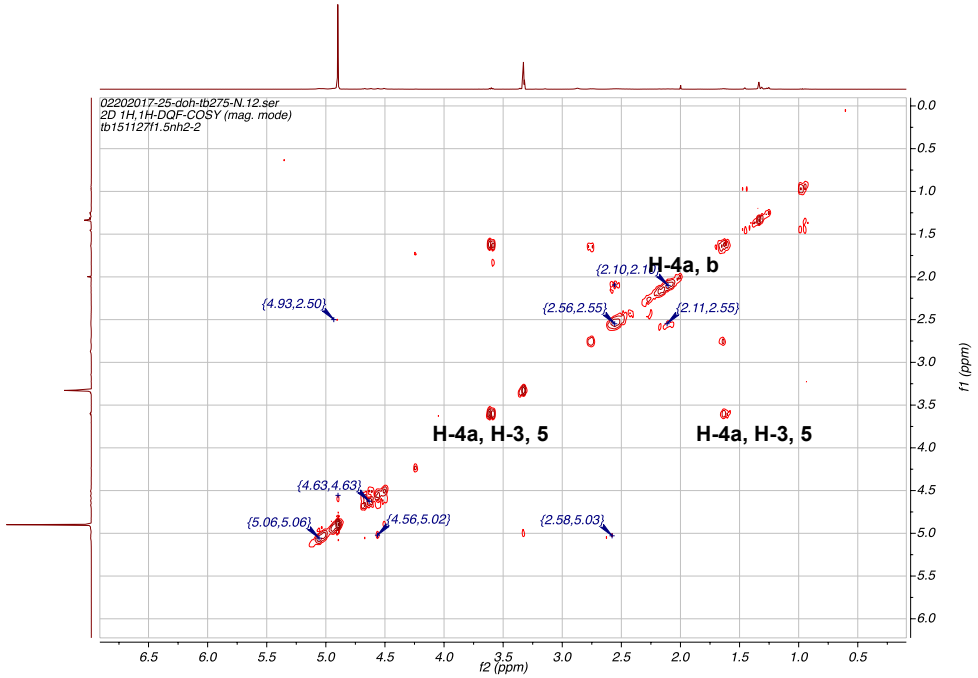
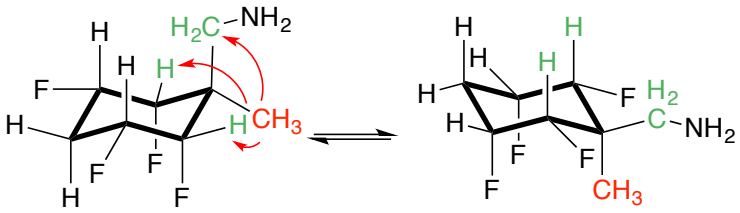
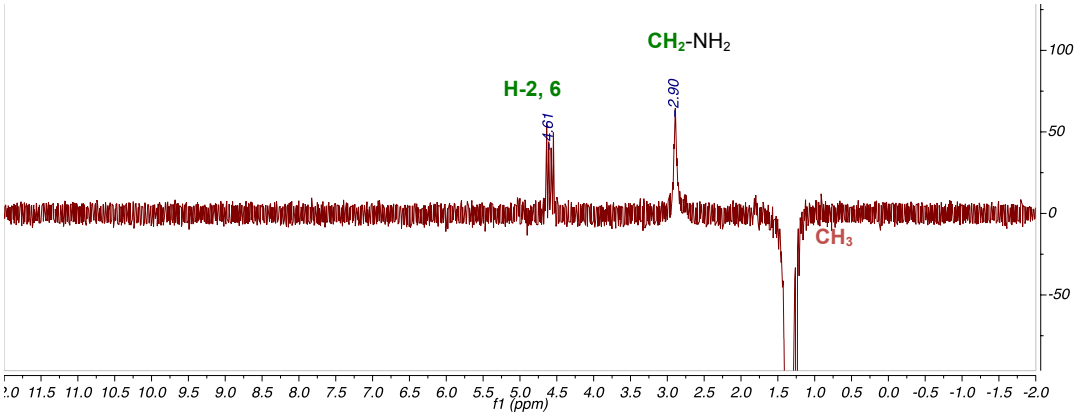
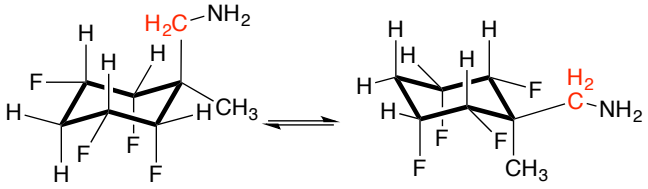


Figure 1: Compound 5.7.a: A) ^{1}H (500 MHz, MeOD); 2D ^{1}H-DQF-COSY (500 MHz, MeOD)



(C) ***1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of CH_3 at 1.33 ppm***





D) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of CH_2 at 2.86 ppm

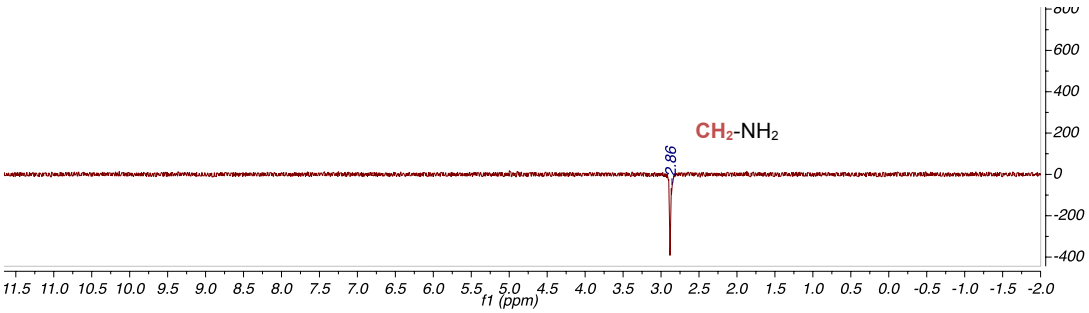
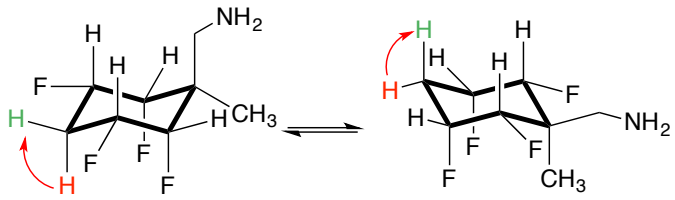
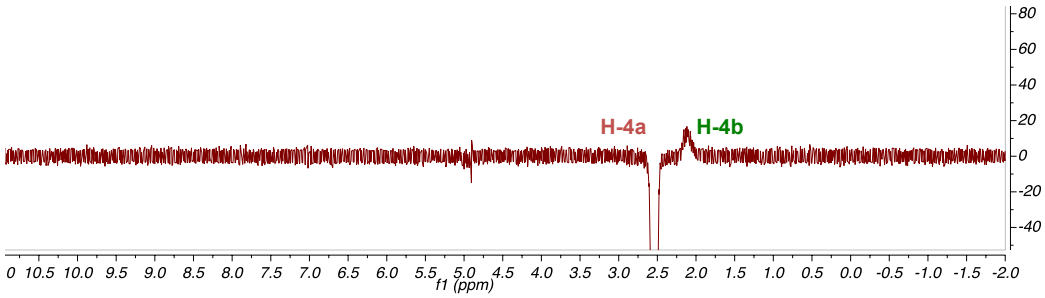
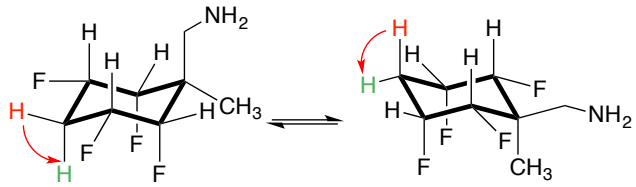


Figure 2: Compound 5.7.a: C) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of CH_3 at 1.33 ppm;D) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of CH_2 at 2.86 ppm



E) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of H-4$_a$ at 2.51 ppm





F) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of H-4$_b$ at 2.25 ppm

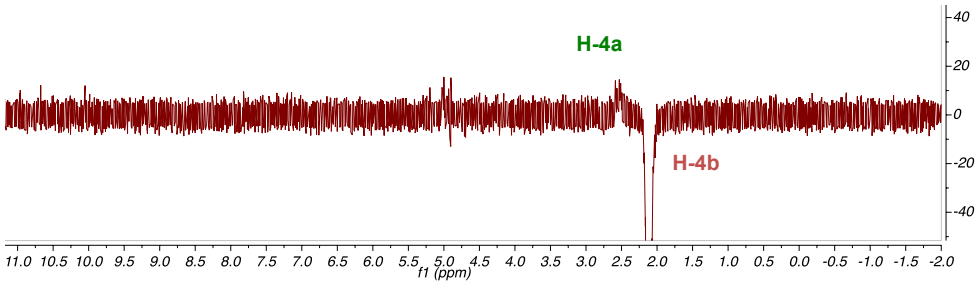
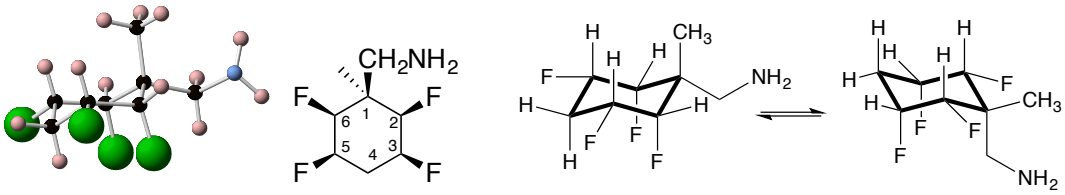
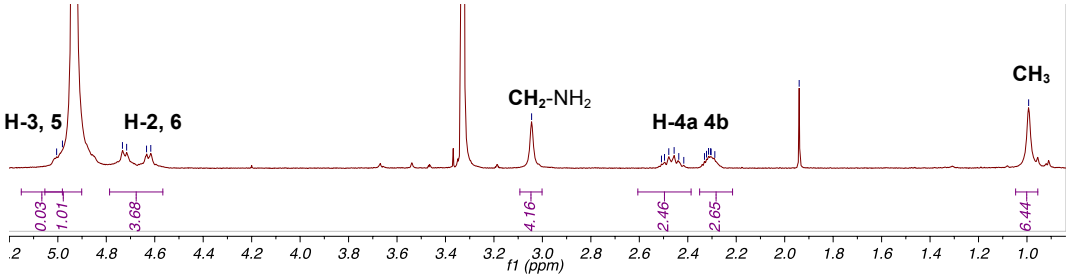


Figure 3: Compound 5.7.a: 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of H-4$_a$ at 2.51 ppm; F) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of H-4$_b$ at 2.25 ppm

7.4.2. (A) ^{1}H NMR; (B) 2D ^{1}H-DQF-COSY; (C) 1D selective ^{1}H, NOESY for 2,3,5,6-tetrafluoro-1-methylcyclohexyl)methanamine (5.7.b)



(A) *^{1}H (500 MHz, MeOD)*



(B) *2D ^{1}H-DQF-COSY (500 MHz, MeOD)*

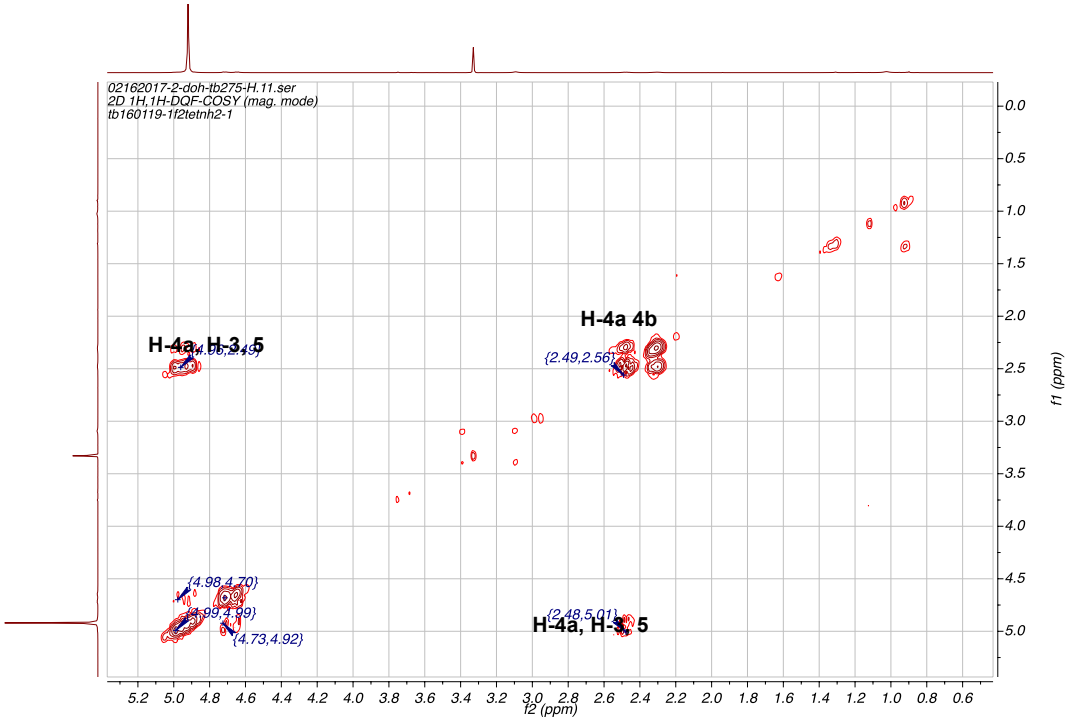
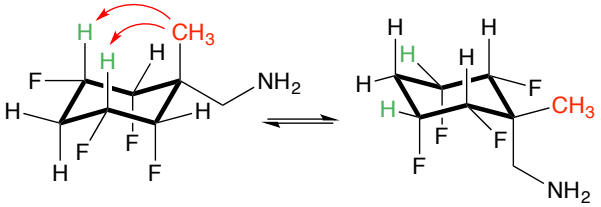
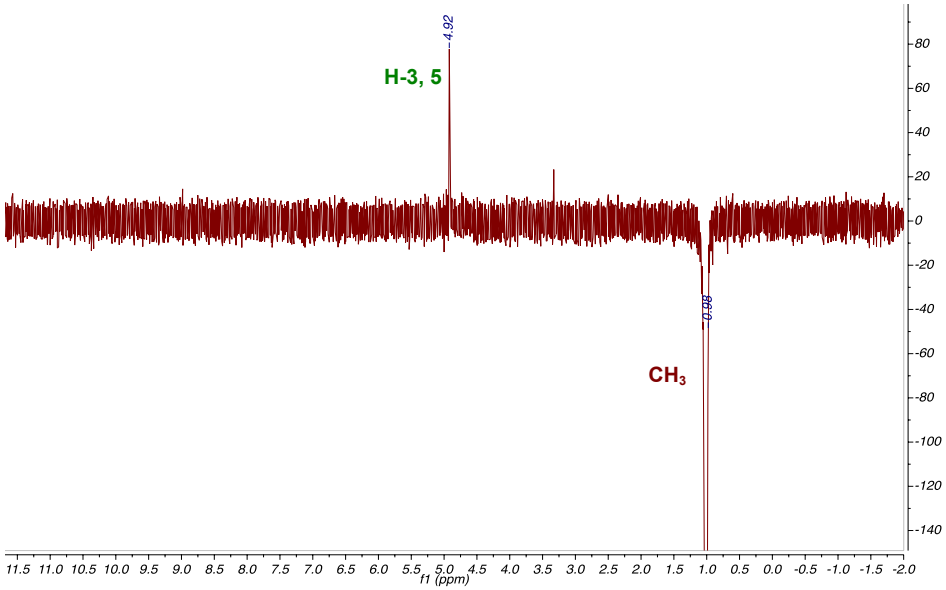
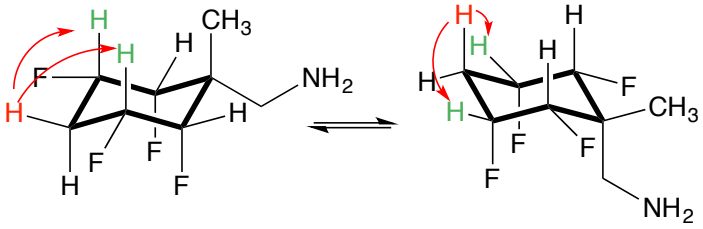


Figure 4: Compound 5.7.b: A) ^{1}H (500 MHz, MeOD); 2D ^{1}H-DQF-COSY (500 MHz, MeOD)



(C) ***1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of CH_3 at 0.98 ppm***





D) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of H-4$_b$ at 2.36 ppm

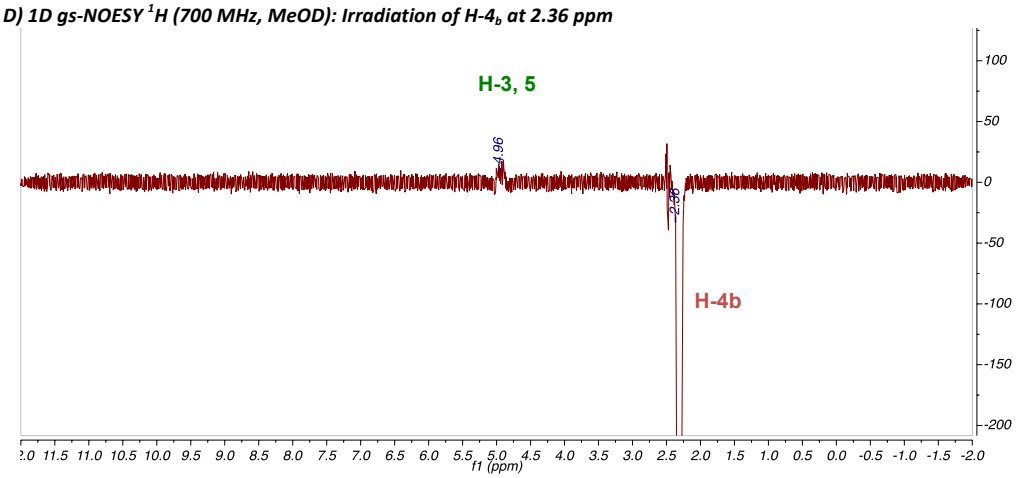
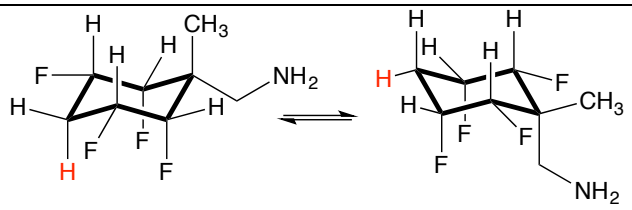
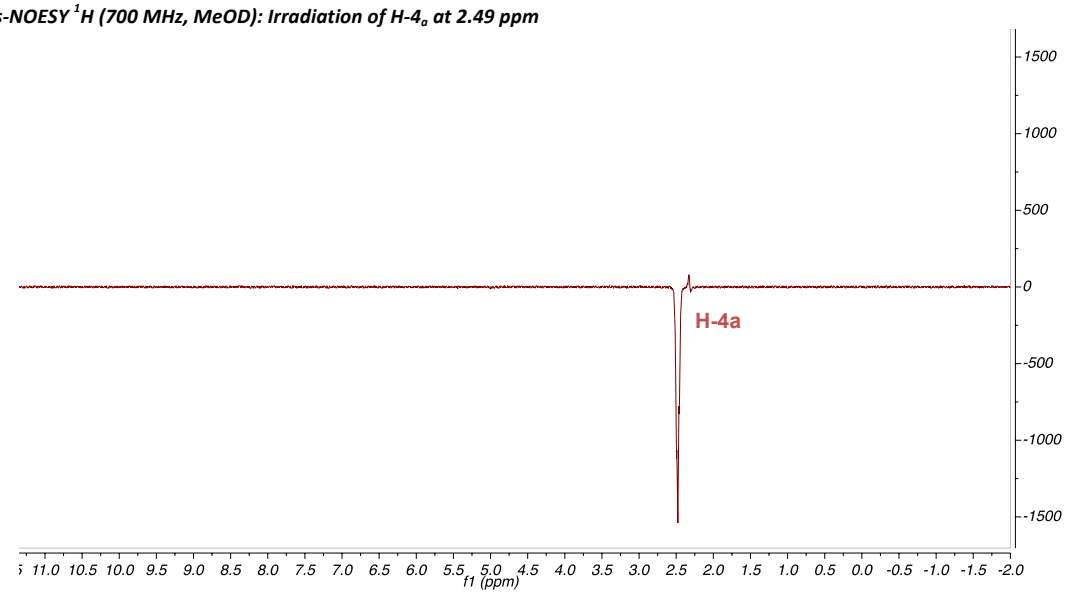
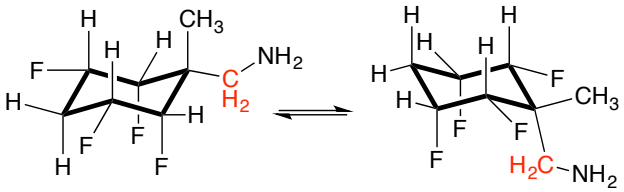


Figure 5: Compound 5.7.b: (C) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of CH_3 at 0.98 ppm; D) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of H-4$_b$ at 2.36 ppm



E) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of H-4$_a$ at 2.49 ppm





F) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of CH$_2$ at 3.09 ppm

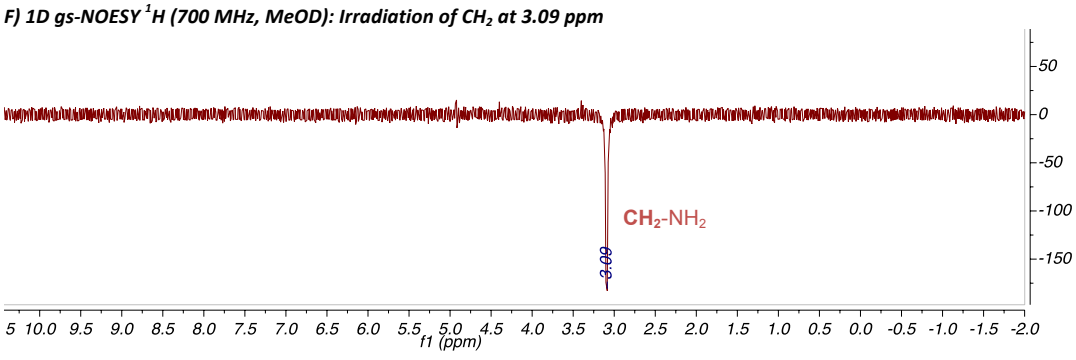
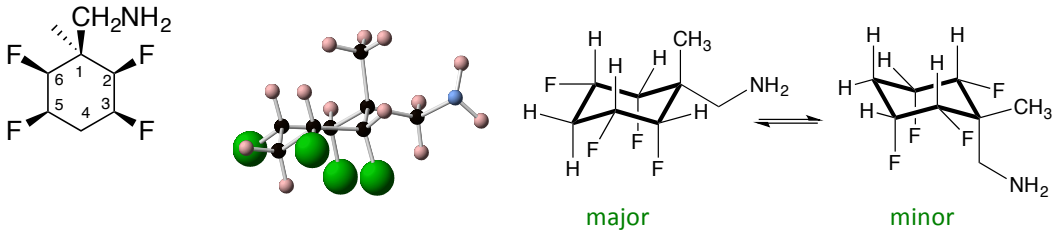


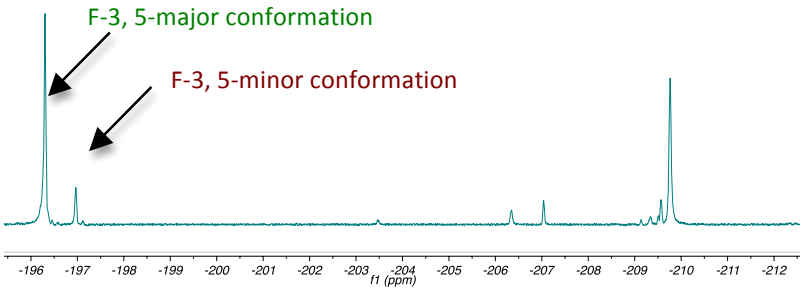
Figure 6: Compound 5.7.b: E) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of H-4$_a$ at 2.49 ppm; F) 1D gs-NOESY ^{1}H (700 MHz, MeOD): Irradiation of CH$_2$ at 3.09 ppm

7.4.3. VT NMR experiments for 2,3,5,6-tetrafluoro-1-methylcyclohexyl)methanamine (5.7.b)



A) ^{19}F NMR with ^{1}H decoupling at rt (700 MHz, MeOD):

B) ^{19}F NMR with ^{1}H decoupling at -40 °C (700 MHz,MeOD):



C)

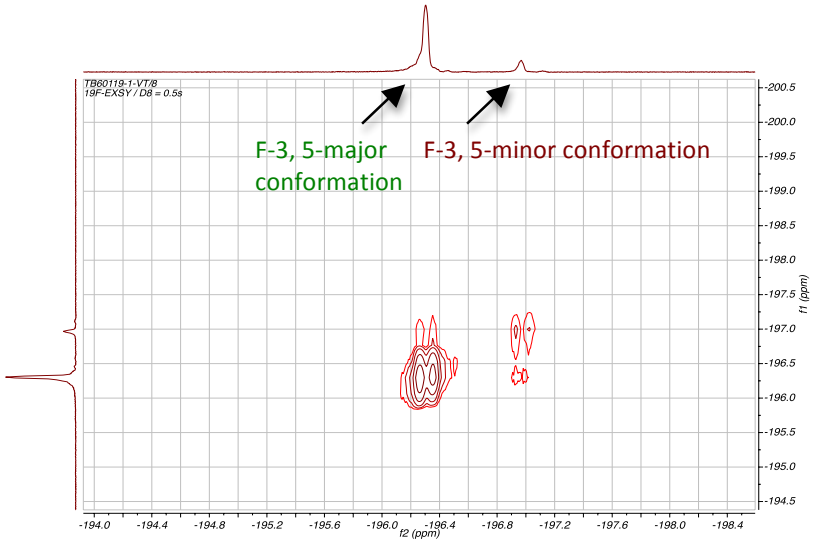
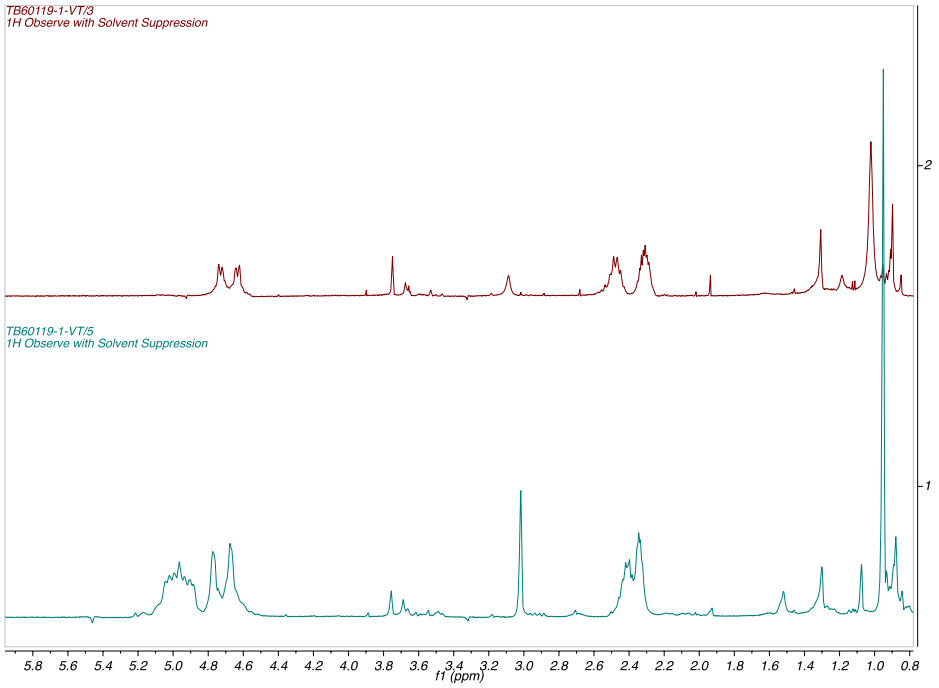


Figure 7: Compound 5.7.b: A) ^{19}F NMR with ^{1}H decoupling at rt (700 MHz, MeOD); ^{19}F NMR with ^{1}H decoupling at -40 °C (700 MHz,MeOD); ^{19}F, ^{1}H HMBC at -40 °C.

D) ^{1}H NMR at rt (red spectra) and at -40 °C (blue spectra), (700 MHz, MeOD):



E) ^{1}H, ^{19}F-HMBC NMR (700 MHz, MeOD):

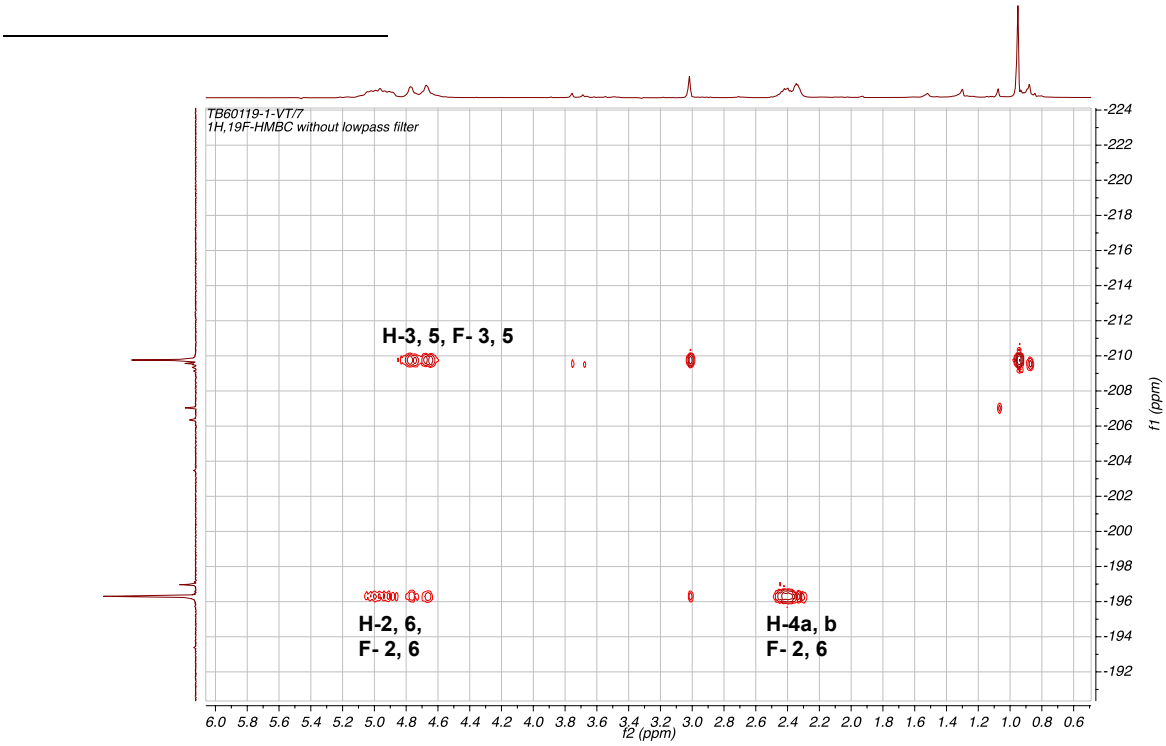


Figure 8: Compound 5.7.b: D) ^{1}H NMR at rt (red spectra) and at -40 °C (blue spectra), (700 MHz, MeOD); E) ^{1}H, ^{19}F-HMBC NMR (700 MHz, MeOD).

7.5. References

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